OIPE IAP41
FEB 14 2007
PATENT & TRADEMARK OFFICE

02-16-07

Attorney's Docket No.: 17080-002002 / 601B

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: John R. McDonald et al.	Art Unit	: 1647
Patent No.	: 7,157,418	Examiner	: Robert S. Landsman
Issue Date	: January 2, 2007	Conf. No.	: 3887
Serial No.	: 09/360,242		
Filed	: July 22, 1999		
Title	: METHODS AND COMPOSITIONS FOR TREATING SECONDARY TISSUE DAMAGE AND OTHER INFLAMMATORY CONDITIONS AND DISORDERS		

Attn: Certificate of Correction Branch
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

TRANSMITTAL LETTER

Dear Sir:

Transmitted herewith are a Request for a Certificate of Correction pursuant to C.F.R. § 1.322 & 1.323 (11 pages), Certificate of Correction Form PTO-1050 (8 pages), a copy of the Preliminary Amendment mailed on October 18, 1999 (5 pages) with date-stamped postcard (1 page), a copy of the Election, Amendment and Response to Notice to Comply mailed on December 13, 1999 (11 pages) with date-stamped postcard (1 page), a copy of the Supplemental Amendment mailed on September 11, 2000 (4 pages) with date-stamped postcard (1 page), a copy of the Preliminary Amendment with RCE filed on February 10, 2006 (60 pages), a copy of Form PTO-1449 initialed by the Examiner on December 18, 2000 (7 pages), a copy of Form PTO-1449 initialed by the Examiner on July 12, 2006 (1 page), a copy of the Issue Classification form signed by the Examiner on July 29, 2006 (1 page), and a return postcard for filing in connection with the above-identified application.

One or more of the errors sought to be corrected were made by applicant, and a check for $100 is enclosed to cover the required fee of 37 CFR §1.20(a).

☒ The Commissioner is hereby authorized to charge any fees that may be due in connection with this paper or with this application during its entire pendency to Deposit Account No. 06-1050. A duplicate of this sheet is enclosed.

Respectfully submitted,

Stephanie Seidman
Reg. No. 33,779

Attorney Docket No. 17080-002002 / 601B
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Certificate
FEB 22 2007
of Correction

CERTIFICATE OF MAILING BY "EXPRESS MAIL"
"Express Mail" Mailing Label Number **EV 740125113 US**
Date of Deposit **February 14, 2007**
I hereby certify that this paper is being deposited with the United States Postal "Express Mail Post Office to Addressee" Service under 37 CFR §1.10 on the date indicated above and is addressed to: Commissioner for Patents, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA, 22313-1450.

Stephanie Seidman

FEB 22 2007

OIPE IAP41
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PATENT & TRADEMARK OFFICE

Attorney's Docket No.: 17080-002002 / 601B

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: John R. McDonald et al.	Art Unit	: 1647
Patent No.	: 7,157,418	Examiner	: Robert S. Landsman
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Title	: METHODS AND COMPOSITIONS FOR TREATING SECONDARY TISSUE DAMAGE AND OTHER INFLAMMATORY CONDITIONS AND DISORDERS		

Attn.: Certificate of Corrections Branch
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

TRANSMITTAL OF REQUEST FOR CERTIFICATE OF CORRECTION

Dear Sir:

Pursuant to 37 C.F.R. § 1.322 and 1.323, the patentee respectfully requests that a Certificate of Correction be issued for the above referenced patent to correct the following errors:

IN THE TITLE PAGES:

In Item [57] ABSTRACT, please delete the "a" between "ligand" and "chemokine";

in Item [57] ABSTRACT, please replace "neutrophiles" with —neutrophils—;

in Item [56] *References Cited* please add to the list of OTHER PUBLICATIONS —Kreitman and Pastan, *Semin. Cancer Biol. 6*(5):297-306 (1995).—;

in Item [56] *References Cited* please add to the list of OTHER PUBLICATIONS —Kreitman, R.J., et al., Recombinant toxins, *Adv. Pharmacol., 28*:193-219 (1994).—;

in Item [56] *References Cited* please add to the list of OTHER PUBLICATIONS —Medh, J.D., et al., *J. Biol. Chem., 270*:536-540 (1995).—;

in Item [56] *References Cited* please add to the list of OTHER PUBLICATIONS —Puri, *Toxicol. Pathol. 27*:53-57 (1999).—;

in Item [56] *References Cited* please add to the list of OTHER PUBLICATIONS

02/16/2007 BABRAHA1 00000037 7157418
01 FC:1811 100.00 OP

CERTIFICATE OF MAILING BY "EXPRESS MAIL"
"Express Mail" Mailing Label Number **EV 740125113 US**
Date of Deposit **February 14, 2007**
I hereby certify that this paper is being deposited with the United States Postal "Express Mail Post Office to Addressee" Service under 37 CFR §1.10 on the date indicated above and is addressed to: Commissioner for Patents, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA, 22313-1450.

Stephanie Seidman

FEB 22 2007

—Sawada, M., et al., *Neurosci. Lett., 160*:131-4 (1993).—;

in Item [56] *References Cited* please add to the list of OTHER PUBLICATIONS

—Stirpe, F., et al., *J. Biol. Chem., 255*:6947-6953 (1980).—;

in Item [56] *References Cited* please add to the list of OTHER PUBLICATIONS

—Ugoccioni, M., et al., *J. Exp. Med., 183*:2379-84 (1996).—;

in Item [56] *References Cited* please add to the list of OTHER PUBLICATIONS

—Zheng, G., et al., *J. Histochem. Cytochem., 42*:531-42 (1994).—;

in Item [56] References Cited, in OTHER PUBLICATIONS:

in EMBL database ID HS1301003, please replace "(Lingkine)" with —(Lungkine) —;

in Hesselgesser et al., please replace "Chernokine" with —Chemokine—;

in Richmond et al., please replace "chernokine/chernokine receptor" with —chemokine/chemokine receptor—; and

in Signoret et al., please replace "Chernokine" with —Chemokine—.

IN THE SPECIFICATION:

At column 1, line 24, please insert —FIELD OF THE INVENTION The present invention relates to therapeutic compositions and their use in treatment of disease states. More particularly, compounds, compositions and methods for treating disease states associated with proliferation, migration and physiological activity of cells involved in inflammatory responses, including, but not limited to, secondary tissue damage, are provided. —;

at column 14, line 43, please replace "FIG. 1 is a schematic drawing" with —FIG. 1A-1C presents schematic drawings—;

at column 14, line 56, please insert —(also designated herein pOPL2)— between "pGEMEX-SAP" and "encoding";

at column 14, lines 59-60, please replace "map of a conjugate MCP-3-AM-Shiga-A1" with —map of a plasmid, designated pOPL1, encoding the conjugate MCP-3-AM-Shiga-A1, which was—;

FEB 2 2 2007

at column 14, lines 62-63, please replace "map of a conjugate MCP-1-AM-SAP" with —map of a plasmid, designated pOPL106, encoding the conjugate MCP-1-AM-SAP—;

at column 14, lines 65-66, please replace "map of a conjugate MCP3-AM-Shiga-A1" with —map of a plasmid, designated pOPL101, encoding the conjugate MCP-3-AM-Shiga-A1—;

at column 16, line 56, please delete "ALP,";

at column 32, line 25, please delete "of";

at column 57, line 30, please insert —)— between "1986" and ".";

at column 57, line 51, please replace "Ed." with —ed. —;

at column 68, line 56, please replace "MIP-1 alpha" with —MIP-1α—; and

at column 69, line 13, please insert —which— between "mice" and "predictably".

IN THE CLAIMS:

Please replace Claims 5, 11, 18, 20, 25, 27, 28, 31, 32, 40, 45, 48, 50 and 55 with the following Claims:

5. The method of ~~claims~~ claim 1, wherein the activated, proliferating or migrating immune cells occur in a disorder or disease state that is selected from the group consisting of CNS injury, CNS inflammatory diseases, neurodegenerative disorders, heart disease, inflammatory eye diseases, inflammatory bowel diseases, inflammatory joint diseases, inflammatory kidney or renal diseases, inflammatory lung diseases, inflammatory nasal diseases, inflammatory thyroid diseases, inflammatory responses associated with bacterial or viral infections and cytokine-regulated cancers.

11. The method of claim 1, wherein the conjugate comprises the following components: ~~(chemokine receptor targeting agent)n, (L)q and (targeted agent)m~~ (chemokine receptor targeting agent)$_n$, (L)$_q$ and (targeted agent)$_m$, wherein:

L is a linker for linking the chemokine receptor targeting agent to a targeted agent;

chemokine receptor targeting agent is any moiety that selectively binds to a chemokine receptor and effects internalization of the conjugate;

m and n, which are selected independently, are at least 1; and

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q is 0 or more as long as the resulting conjugate binds to the targeted receptor, is internalized and delivers the targeted agent;

the resulting conjugate binds to a receptor that interacts with and internalizes a chemokine, whereby the targeted agent(s) is internalized in a cell bearing the receptor; and

when the conjugate contains a plurality of targeted agents, the targeted agents are the same or different, and when the conjugate contains a plurality of chemokine receptor targeting agents, the targeting agents are the same or different.

18. The method of claim 11, [[when]] wherein the chemokine receptor targeting agent and targeted agent are linked directly via a covalent or ionic linkage.

20. The method of claim 19, wherein the linker is a peptide linkage, a polypeptide or [[is]] a chemical linker.

25. The method of claim 22, wherein the chemokine is selected from the group consisting of IL-8, GCP-2, GRO-α, GRO-β, GRP-γ, ENA-78, PBP, CTAP III, NAP-2, LAPF-4, MIG, IP-10, SDF-1α, SDF-1β, SDF-2, MCP-1, MCP-2, MCP-3, [[MCP4]] MCP-4, MCP-5, MIP-1α, MIP-1β, MIP-1γ, MIP-2, MIP-2α, MIP-3α, MIP-3β, MIP-4, MIP-5, MDC, HCC-1, [[LD78μ]] LD78β, eotaxin-1, eotaxin-2, I-309, SCYA17, TARC, RANTES, DC-CK-1, lymphotactin and fractalkine.

27. The method of claim 1, wherein the chemokine receptor is selected from the group consisting of CXCR-1, CXCR-2, CXCR-3, CXCR-4, CXCR-5, CCR-1, CCR-2A, CCR-2B, CCR-3, [[CCR4]] CCR-4, CCR-5, [[CCR4]] CCR-6, CCR-7, CCR-8, [[CCR-8,]] CX3CR-1, XCR1, Duffy antigen receptor for chemokines (DARC) and CD97.

28. The method of claim 22, wherein the chemokine receptor is selected from the group consisting of DARC, CXCR-1, CXCR-2, CXCR-3, CXCR-4, CCR-1, CCR-2A, CCR-2B, CCR-3, [[CCR4]] CCR-4, CCR-5, [[CCR6]] CCR-6, CCR-7, CCR-8, CX3CR-1, and CD97.

31. A method for inhibiting proliferation or migration of activated immune effector cells, comprising contacting immune effector cells with a conjugate that comprises a targeted agent or a portion thereof and a chemokine receptor targeting agent, whereby activation or proliferation of the immune effector cells is inhibited, wherein:

the targeted agent or portion thereof is a toxin;

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the chemokine receptor targeting agent is a chemokine or a fragment [[of]] thereof that binds to a chemokine receptor and internalizes the targeted agent; and

the conjugate binds to a chemokine receptor resulting in internalization of the targeted agent in cells bearing the receptor.

32. The method of claim 31, wherein the conjugate comprises the following components: ~~(chemokine receptor targeting agent)n, (L)q and (targeted agent)m~~ (chemokine receptor targeting agent)$_n$, (L)$_q$ and (targeted agent)$_m$, wherein:

L is a linker for linking the chemokine or fragment thereof to a targeted agent;

m and n, which are selected independently, are at least 1; and

q is 0 or more as long as the resulting conjugate binds to the targeted receptor, is internalized and delivers the targeted agent;

the resulting conjugate binds to a receptor that interacts with and internalizes a chemokine, whereby the targeted agent(s) is internalized in a cell bearing the receptor; and

when the conjugate contains a plurality of targeted agents, the targeted agents are the same or different, and when the conjugate contains a plurality of chemokine receptor targeting agents, the targeting agents are the same or different.

40. The method of claim 29, wherein the chemokine is selected from the group consisting of IL-8, GCP-2, GRO-α, GRO-β, GRP-γ, ENA-78, PBP, CTAP III, NAP-2, LAPF-4, MIG, IP-10, SDF-1α, SDF-1β, SDF-2, MCP-1, MCP-2, MCP-3, [[MCP4]] MCP-4, MCP-5, MIP-1α, MIP-1β, MIP-1γ, MIP-2, MIP-2α, MIP-3α, MIP-3β, MIP-4, MIP-5, MDC, HCC-1, [[LD78μ]] LD78β, eotaxin-1, eotaxin-2, I-309, SCYA17, TARC, RANTES, DC-CK-1, lymphotactin, and fractalkine.

45. A method of preparing a candidate compound for treating a disease or disorder involving activated immune cells ~~an inflammatory response~~, comprising:

identifying immune cells that are activated in the disease or disorder;

identifying chemokine receptors expressed on the cells; and

preparing a conjugate or plurality thereof containing a toxin linked to a chemokine or a plurality of chemokines that specifically bind to the identified chemokine receptors and effect or facilitate internalization of the toxin into the cells.

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48. The method of claim 21, wherein the chemokine receptor targeting agent is selected from the group consisting of IL-8, GCP-2, GRO-α, GRO-β, GRP-γ, ENA-78, PBP, CTAP III, NAP-2, LAPF-4, MIG, IP-10, SDF-1α, SDF-1β, SDF-2, MCP-1, MCP-2, MCP-3, [[MCP4]] MCP-4, MCP-5, MIP-1α, MIP-1β, MIP-1γ, MIP-2, MIP-2α, MIP-3α, MIP-3β, MIP-4, MIP-5, MDC, HCC-1, LD78β, eotaxin-1, eotaxin-2, I-309, SCYA17, TARC, RANTES, DC-CK-1, lymphotactin, and fractalkine.

50. The method of claim 45, wherein the chemokine is selected from the group consisting of IL-8, GCP-2, GRO-α, GRO-β, GRP-γ, ENA-78, PBP, CTAP III, NAP-2, LAPF-4, MIG, IP-10, SDF-1α, SDF-1β, SDF-2, MCP-1, MCP-2, MCP-3, [[MCP4]] MCP-4, MCP-5, MIP-1α, MIP-1β, MIP-1γ, MIP-2, MIP-2α, MIP-3α, MIP-3β, MIP-4, MIP-5, MDC, HCC-1, LD78β, eotaxin-1, eotaxin-2, I-309, SCYA17, TARC, RANTES, DC-CK-1, lymphotactin, and fractalkine.

55. The method of ~~claim 29~~ claim 45, further comprising:

contacting the immune cells with the conjugate or plurality thereof, whereby the toxin is internalized.

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REMARKS

A Certificate of Correction (Form PTO-1050) incorporating the above changes is included with this Request. Since not all the errors are those of the Patent Office, a check is enclosed to cover the required fee. If it is determined that the fee amount is incorrect or if the check is missing, the Office is hereby authorized to charge the fee to Deposit Account No. 06-1050.

IN THE TITLE PAGES:

This Certificate of Correction seeks to correct obvious spelling and typographical errors in the ABSTRACT, Item [57]. Deletion of the "a" between "ligand" and "chemokine" seeks to render the phrase grammatically correct. Additionally, the ABSTRACT is amended to correct a spelling error introduced by the PTO by replacing "neutrophiles" with —neutrophils—. The basis for this amendment is found on page 4, line 11 of the Preliminary Amendment, mailed on October 18, 1999. Copies of the Preliminary Amendment and the date-stamped postcard are attached herewith as evidence.

This Certificate of Correction seeks to correct obvious spelling and typographical errors in the "OTHER PUBLICATIONS" section of the References Cited, Item [56] introduced by the PTO. This Certificate of Correction further seeks to correct errors in the OTHER PUBLICATIONS section of Item [56] wherein references Kreitman and Pastan (1995), Kreitman et al. (1994), Medh et al. (1995), Puri (1999), Sawada et al. (1993), Stirpe et al. (1980), and Zheng et al. (1994) were omitted from the list of other publications in the issued patent. The corrections find basis in Form PTO-1449, which was considered and initialed by the Examiner on December 18, 2000 and sent back to the Applicant by the Examiner accompanying an Office Action dated December 20, 2000. A copy of the initialed Form PTO-1449 is included herewith as evidence.

This Certificate of Correction also seeks to correct an error in the OTHER PUBLICATIONS section of Item [56] wherein reference Ugoccioni et al. (1996) was omitted from the list of other publications in the issued patent. The corrections find basis in Form PTO-1449, which was considered and initialed by the Examiner on July 12, 2006 and sent back to the

FEB 2 2 2007

Applicant by the Examiner accompanying an Office Communication dated July 17, 2006. A copy of the initialed Form PTO-1449 is included herewith as evidence.

IN THE SPECIFICATION:

This Certificate of Correction seeks to correct an error in the Specification wherein the section entitled "FIELD OF THE INVENTION" was omitted from the Specification in the issued patent. Basis for the correction can be found in the application as originally filed at page 1, lines 20-26.

This Certificate of Correction further seeks to correct obvious typographical, grammatical and formatting errors in the Specification. Additionally, this Certificate of Correction seeks to correct errors introduced by the PTO. For example, corrections to the BRIEF DESCRIPTION OF THE FIGURES section of the Specification at column 14 seek to incorporate amendments made to the Specification, found on pages 1 and 2 of the Supplemental Amendment mailed on September 11, 2000. Copies of the Supplemental Amendment and the date-stamped postcard are attached herewith as evidence. The correction at column 16 seeks to incorporate an amendment made to the Specification, found on page 2, line 8 of the Preliminary Amendment mailed on October 18, 1999. Copies of the Preliminary Amendment and the date-stamped postcard are attached herewith as evidence. The correction at column 32 seeks to incorporate an amendment made to the Specification, found on page 2, line 11 of the Election, Amendment and Response to Notice to Comply mailed on December 13, 1999. The corrections at column 57 seek to incorporate amendments made to the Specification, found on page 3, lines 1 and 2 of the Election, Amendment and Response to Notice to Comply mailed on December 13, 1999. The correction at column 69 seeks to incorporate an amendment made to the Specification, found on page 3, line 3 of the Election, Amendment and Response to Notice to Comply mailed on December 13, 1999. Copies of the Election, Amendment and Response to Notice to Comply and the date-stamped postcard are attached herewith as evidence.

IN THE CLAIMS:

This Certificate of Correction seeks to correct minor typographical, spelling, and formatting errors in the Claims. Claim 5 is amended to correct the error at column 201, line 41, by replacing "claims" with —claim— to render the phrase grammatically correct.

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Claim 11 is amended to correct the formatting error at column 202, line 26, by replacing "(chemokine receptor targeting agent)n, (L)q and (targeted agent)m" with —(chemokine receptor targeting agent)$_n$, (L)$_q$ and (targeted agent)$_m$— as found in the originally filed application at page 16, lines 7-8.

Claim 18 is amended to correct the error introduced by the PTO at column 18, line 65, by replacing "when" with —wherein— to render the phrase grammatically correct. Basis for this amendment is found on page 6, line 3 of the Preliminary Amendment with RCE filed on February 10, 2006, a copy of which is attached herewith as evidence.

Claim 20 is amended to correct the error at column 203, line 5, by replacing "is" with —a— to render the phrase grammatically correct.

Claim 25 is amended to correct the formatting errors introduced by the PTO at column 203, lines 27 and 29, by replacing "MCP4" with —MCP-4— and "LD78μ" with —LD78β—. Basis for the amendments is found on page 6, line 28 and line 29, respectively, of the Preliminary Amendment with RCE filed on February 10, 2006, a copy of which is attached herewith as evidence.

Claim 27 is amended to correct the error at column 203, line 35, by inserting —is— between "receptor" and "selected" to render the phrase grammatically correct. Claim 27 is further amended to correct the error at column 203, line 38, by deleting "CCR-8" since it is inadvertently listed twice in Claim 27. Claim 27 is further amended to correct the errors introduced by the PTO at column 203, line 37 by replacing the first "CCR4" with —CCR-4— and the second "CCR4" with —CCR-6—. Basis for the latter amendments is found on page 7, line 3 of the Preliminary Amendment with RCE filed on February 10, 2006, a copy of which is attached herewith as evidence.

Claim 28 is amended to correct the formatting errors introduced by the PTO at column 203, line 43, by replacing "CCR4" with —CCR-4— and "CCR6" with —CCR-6—. Basis for the amendments is found on page 7, line 7 of the Preliminary Amendment with RCE filed on February 10, 2006, a copy of which is attached herewith as evidence.

Claim 31 is amended to correct the error at column 203, line 63, by deleting "of" between "fragment" and "thereof" to render the phrase grammatically correct.

FEB 2 2 2007

Claim 32 is amended to correct the formatting error at column 204, line 3, by replacing "(chemokine receptor targeting agent)n, (L)q and (targeted agent)m" with —(chemokine receptor targeting agent)$_n$, (L)$_q$ and (targeted agent)$_m$— as found in the originally filed application at page 16, lines 7-8.

Claim 40 is amended to correct the formatting errors introduced by the PTO at column 204, lines 49 and 51, by replacing "MCP4" with —MCP-4— and "LD78μ" with —LD78β—. Basis for the amendments is found on page 8, lines 22 and 23, respectively, of the Preliminary Amendment with RCE filed on February 10, 2006, a copy of which is attached herewith as evidence.

Claim 45 is amended to correct an obvious typographical error at column 204, line 67, by deleting "an inflammatory response". Claim 45 is further amended to correct an obvious typographical error at column 205, line 3, by inserting —and— after "cells;" and an obvious typographical error at column 205, line 4, by inserting —a— between "containing" and "toxin".

Claim 48 is amended to correct the formatting error introduced by the PTO at column 205, line 20, by replacing "MCP4" with —MCP-4—. Basis for the amendment can be found on page 9, line 17 of the Preliminary Amendment with RCE filed on February 10, 2006, a copy of which is attached herewith as evidence.

Claim 50 is amended to correct the formatting error introduced by the PTO at column 206, line 5, by replacing "MCP4" with —MCP-4—. Basis for the amendment can be found on page 9, line 29 of the Preliminary Amendment with RCE filed on February 10, 2006, a copy of which is attached herewith as evidence.

Claim 55 is amended to correct a claim dependency error introduced by the PTO at column 206, line 24, by replacing "claim 29" with —claim 45—. Basis for the amendment can be found on page 10, line 8 of the Preliminary Amendment with RCE filed on February 10, 2006 wherein claim 96, which corresponds claim 55 of the issued patent, depends from claim 86, which corresponds to claim 45 of the issued patent. Claim correspondence finds basis in the renumbering of claims found on the Issue Classification form signed by the Examiner on July 29, 2006 and sent to the Applicant by the Examiner accompanying a Notice of Allowance and Fee(s)

FEB 22 2007

Due dated August 8, 2006. Copies of the Preliminary Amendment with RCE and the Issue Classification form are attached herewith as evidence.

Accordingly, none of the requested changes constitute new matter. Patentee respectfully requests correction of errors by issuance of a Certificate of Correction.

Respectfully submitted,

Stephanie Seidman
Reg. No. 33,779

Attorney Docket No. 17080-002002 / 601B
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Email: seidman@fr.com

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FEB 22 2007

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UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. .: 7,157,418
APPLICATION NO .: 09/360,242
DATED .: JANUARY 2, 2007
INVENTOR(S) .: JOHN R. MCDONALD AND PHILLIP J. COGGINS, PH.D.

It is certified that an error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

IN THE TITLE PAGES:

In Item [57] ABSTRACT, please delete the "a" between "ligand" and "chemokine"
in Item [57] ABSTRACT, please replace "neutrophiles" with —neutrophils—
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in Item [56] *References Cited* please add to the list of OTHER PUBLICATIONS —Puri, *Toxicol. Pathol. 27*:53-57 (1999).—
in Item [56] *References Cited* please add to the list of OTHER PUBLICATIONS —Sawada, M., et al., *Neurosci. Lett., 160*:131-4 (1993).—
in Item [56] *References Cited* please add to the list of OTHER PUBLICATIONS —Stirpe, F., et al., *J. Biol. Chem., 255*:6947-6953 (1980).—
in Item [56] *References Cited* please add to the list of OTHER PUBLICATIONS —Ugoccioni, M., et al., *J. Exp. Med., 183*:2379-84 (1996).—
in Item [56] *References Cited* please add to the list of OTHER PUBLICATIONS —Zheng, G., et al., *J. Histochem. Cytochem., 42*:531-42 (1994).—
in Item [56] *References Cited*, in OTHER PUBLICATIONS:
in EMBL database ID HS1301003, please replace "(Lingkine)" with —(Lungkine) —

MAILING ADDRESS OF SENDER:

Stephanie Seidman
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P.O. Box 1022
Minneapolis, Minnesota 55440-1022

FEB 22 2007

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UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. .: 7,157,418
APPLICATION NO .: 09/360,242
DATED .: JANUARY 2, 2007
INVENTOR(S) .: JOHN R. MCDONALD AND PHILLIP J. COGGINS, PH.D.

It is certified that an error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

in Hesselgesser et al., please replace "Chernokine" with —Chemokine—
in Richmond et al., please replace "chernokine/chernokine receptor" with —chemokine/chemokine receptor—
in Signoret et al., please replace "Chernokine" with —Chemokine—

IN THE SPECIFICATION:

At column 1, line 24, please insert —FIELD OF THE INVENTION The present invention relates to therapeutic compositions and their use in treatment of disease states. More particularly, compounds, compositions and methods for treating disease states associated with proliferation, migration and physiological activity of cells involved in inflammatory responses, including, but not limited to, secondary tissue damage, are provided. —
at column 14, line 43, please replace "FIG. 1 is a schematic drawing" with —FIG. 1A-1C presents schematic drawings—
at column 14, line 56, please insert —(also designated herein pOPL2)— between "pGEMEX-SAP" and "encoding"
at column 14, lines 59-60, please replace "map of a conjugate MCP-3-AM-Shiga-A1" with —map of a plasmid, designated pOPL1, encoding the conjugate MCP-3-AM Shiga-A1, which was—
at column 14, lines 62-63, please replace "map of a conjugate MCP-1-AM-SAP" with —map of a plasmid, designated pOPL106, encoding the conjugate MCP-1-AM-SAP—

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P.O. Box 1022
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UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

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APPLICATION NO .: 09/360,242
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INVENTOR(S) .: JOHN R. MCDONALD AND PHILLIP J. COGGINS, PH.D.

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at column 14, lines 65-66, please replace "map of a conjugate MCP3-AM-Shiga-A1" with —map of a plasmid, designated pOPL101, encoding the conjugate MCP-3-AM Shiga-A1—
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at column 32, line 25, please delete "of"
at column 57, line 30, please insert —)— between "1986" and "."
at column 57, line 51, please replace "Ed." with —ed. —
at column 68, line 56, please replace "MIP-1 alpha" with —MIP-1α—
at column 69, line 13, please insert —which— between "mice" and "predictably"

IN THE CLAIMS:

Please replace Claims 5, 11, 18, 20, 25, 27, 28, 31, 32, 40, 45, 48, 50 and 55 with the following Claims:

5. The method of claim 1, wherein the activated, proliferating or migrating immune cells occur in a disorder or disease state that is selected from the group consisting of CNS injury, CNS inflammatory diseases, neurodegenerative disorders, heart disease, inflammatory eye diseases, inflammatory bowel diseases, inflammatory joint diseases, inflammatory kidney or renal diseases, inflammatory lung diseases, inflammatory nasal diseases, inflammatory thyroid diseases, inflammatory responses associated with bacterial or viral infections and cytokine-regulated cancers.

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UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. .: 7,157,418
APPLICATION NO .: 09/360,242
DATED .: JANUARY 2, 2007
INVENTOR(S) .: JOHN R. MCDONALD AND PHILLIP J. COGGINS, PH.D.

It is certified that an error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

11. The method of claim 1, wherein the conjugate comprises the following components: (chemokine receptor targeting agent)$_n$, (L)$_q$ and (targeted agent)$_m$, wherein:
L is a linker for linking the chemokine receptor targeting agent to a targeted agent;
chemokine receptor targeting agent is any moiety that selectively binds to a chemokine receptor and effects internalization of the conjugate;
m and n, which are selected independently, are at least 1; and
q is 0 or more as long as the resulting conjugate binds to the targeted receptor, is internalized and delivers the targeted agent;
the resulting conjugate binds to a receptor that interacts with and internalizes a chemokine, whereby the targeted agent(s) is internalized in a cell bearing the receptor; and
when the conjugate contains a plurality of targeted agents, the targeted agents are the same or different, and when the conjugate contains a plurality of chemokine receptor targeting agents, the targeting agents are the same or different.

18. The method of claim 11, wherein the chemokine receptor targeting agent and targeted agent are linked directly via a covalent or ionic linkage.

20. The method of claim 19, wherein the linker is a peptide linkage, a polypeptide or a chemical linker.

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INVENTOR(S) .: JOHN R. MCDONALD AND PHILLIP J. COGGINS, PH.D.

It is certified that an error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

25. The method of claim 22, wherein the chemokine is selected from the group consisting of IL-8, GCP-2, GRO-α, GRO-β, GRP-γ, ENA-78, PBP, CTAP III, NAP-2, LAPF-4, MIG, IP-10, SDF-1α, SDF-1β, SDF-2, MCP-1, MCP-2, MCP-3, MCP-4, MCP-5, MIP-1α, MIP-1β, MIP-1γ, MIP-2, MIP-2α, MIP-3α, MIP-3β, MIP-4, MIP-5, MDC, HCC-1, LD78β, eotaxin-1, eotaxin-2, I-309, SCYA17, TARC, RANTES, DC-CK-1, lymphotactin and fractalkine.

27. The method of claim 1, wherein the chemokine receptor is selected from the group consisting of CXCR-1, CXCR-2, CXCR-3, CXCR-4, CXCR-5, CCR-1, CCR-2A, CCR-2B, CCR-3, CCR-4, CCR-5, CCR-6, CCR-7, CCR-8, CX3CR-1, XCR1, Duffy antigen receptor for chemokines (DARC) and CD97.

28. The method of claim 22, wherein the chemokine receptor is selected from the group consisting of DARC, CXCR-1, CXCR-2, CXCR-3, CXCR-4, CCR-1, CCR-2A, CCR-2B, CCR-3, CCR-4, CCR-5, CCR-6, CCR-7, CCR-8, CX3CR-1, and CD97.

31. A method for inhibiting proliferation or migration of activated immune effector cells, comprising contacting immune effector cells with a conjugate that comprises a targeted agent or a portion thereof and a chemokine receptor targeting agent, whereby activation or proliferation of the immune effector cells is inhibited, wherein:
the targeted agent or portion thereof is a toxin;

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PATENT NO. .: 7,157,418
APPLICATION NO .: 09/360,242
DATED .: JANUARY 2, 2007
INVENTOR(S) .: JOHN R. MCDONALD AND PHILLIP J. COGGINS, PH.D.

It is certified that an error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

the chemokine receptor targeting agent is a chemokine or a fragment thereof that binds to a chemokine receptor and internalizes the targeted agent; and

the conjugate binds to a chemokine receptor resulting in internalization of the targeted agent in cells bearing the receptor.

32. The method of claim 31, wherein the conjugate comprises the following components: (chemokine receptor targeting agent)$_n$, (L)$_q$ and (targeted agent)$_m$, wherein:

L is a linker for linking the chemokine or fragment thereof to a targeted agent;

m and n, which are selected independently, are at least 1; and

q is 0 or more as long as the resulting conjugate binds to the targeted receptor, is internalized and delivers the targeted agent;

the resulting conjugate binds to a receptor that interacts with and internalizes a chemokine, whereby the targeted agent(s) is internalized in a cell bearing the receptor; and

when the conjugate contains a plurality of targeted agents, the targeted agents are the same or different, and when the conjugate contains a plurality of chemokine receptor targeting agents, the targeting agents are the same or different.

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UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. .: 7,157,418
APPLICATION NO .: 09/360,242
DATED .: JANUARY 2, 2007
INVENTOR(S) .: JOHN R. MCDONALD AND PHILLIP J. COGGINS, PH.D.

It is certified that an error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

40. The method of claim 29, wherein the chemokine is selected from the group consisting of IL-8, GCP-2, GRO-α, GRO-β, GRP-γ, ENA-78, PBP, CTAP III, NAP-2, LAPF-4, MIG, IP-10, SDF-1α, SDF-1β, SDF-2, MCP-1, MCP-2, MCP-3, MCP-4, MCP-5, MIP-1α, MIP-1β, MIP-1γ, MIP-2, MIP-2α, MIP-3α, MIP-3β, MIP-4, MIP-5, MDC, HCC-1, LD78β, eotaxin-1, eotaxin-2, I-309, SCYA17, TARC, RANTES, DC-CK-1, lymphotactin, and fractalkine.

45. A method of preparing a candidate compound for treating a disease or disorder involving activated immune cells, comprising:
identifying immune cells that are activated in the disease or disorder;
identifying chemokine receptors expressed on the cells; and
preparing a conjugate or plurality thereof containing a toxin linked to a chemokine or a plurality of chemokines that specifically bind to the identified chemokine receptors and effect or facilitate internalization of the toxin into the cells.

48. The method of claim 21, wherein the chemokine receptor targeting agent is selected from the group consisting of IL-8, GCP-2, GRO-α, GRO-β, GRP-γ, ENA-78, PBP, CTAP III, NAP-2, LAPF-4, MIG, IP-10, SDF-1α, SDF-1β, SDF-2, MCP-1, MCP-2, MCP-3, MCP-4, MCP-5, MIP-1α, MIP-1β, MIP-1γ, MIP-2, MIP-2α, MIP-3α, MIP-3β, MIP-4, MIP-5, MDC, HCC-1, LD78β, eotaxin-1, eotaxin-2, I-309, SCYA17, TARC, RANTES, DC-CK-1, lymphotactin, and fractalkine.

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CERTIFICATE OF CORRECTION

PATENT NO. .: 7,157,418

APPLICATION NO .: 09/360,242

DATED .: JANUARY 2, 2007

INVENTOR(S) .: JOHN R. MCDONALD AND PHILLIP J. COGGINS, PH.D.

It is certified that an error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

50. The method of claim 45, wherein the chemokine is selected from the group consisting of IL-8, GCP-2, GRO-α, GRO-β, GRP-γ, ENA-78, PBP, CTAP III, NAP-2, LAPF-4, MIG, IP-10, SDF-1α, SDF-1β, SDF-2, MCP-1, MCP-2, MCP-3, MCP-4, MCP-5, MIP-1α, MIP-1β, MIP-1γ, MIP-2, MIP-2α, MIP-3α, MIP-3β, MIP-4, MIP-5, MDC, HCC-1, LD78β, eotaxin-1, eotaxin-2, I-309, SCYA17, TARC, RANTES, DC-CK-1, lymphotactin, and fractalkine.

55. The method of claim 45, further comprising:
contacting the immune cells with the conjugate or plurality thereof, whereby the toxin is internalized.

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THE STAMP OF THE U.S. PATENT AND TRADEMARK OFFICE AFFIXED HERETO WILL BE EVIDENCE OF RECEIPT OF THE FOLLOWING (SENT VIA FIRST CLASS, PRIORITY MAIL) ON 12/13/99:

Client #: 25020-601B

Enclosures: TRANSMITTAL LETTER (in duplicate); ELECTION, AMENDMENT and RESPONSE TO NOTICE TO COMPLY WITH REQUIREMENTS; PAPER and DISK COPIES OF SUBSTITUTE SEQUENCE LISTING; VERIFIED STATEMENT; DECLARATION; COPY OF NOTICE TO COMPLY; and RETURN POSTCARD.

Applicant: McDonald *et al.*

Serial #: 09/360,242 **Filed:** July 22, 1999

For: *METHODS AND COMPOSITIONS FOR TREATING SECONDARY TISSUE DAMAGE AND OTHER INFLAMMATORY CONDITIONS AND DISORDERS*

PLEASE STAMP HERE. THANK YOU.

THE STAMP OF THE U.S. PATENT AND TRADEMARK OFFICE AFFIXED HERETO WILL BE EVIDENCE OF RECEIPT OF THE FOLLOWING (SENT VIA FIRST CLASS, PRIORITY MAIL) ON 12/13/99:

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Applicant: McDonald *et al.*

Serial #: 09/360,242 **Filed:** July 22, 1999

For: *METHODS AND COMPOSITIONS FOR TREATING SECONDARY TISSUE DAMAGE AND OTHER INFLAMMATORY CONDITIONS AND DISORDERS*

PLEASE STAMP HERE. THANK YOU.

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: McDONALD et al.

Serial No. 09/360,242

Filed: July 22, 1999

For: *METHODS AND COMPOSITIONS FOR TREATING SECONDARY TISSUE DAMAGE AND OTHER INFLAMMATORY CONDITIONS AND DISORDERS*

Art Unit: 1646

Examiner: Landsman, R.

I hereby certify that this paper is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231, on this date.

12/13/99
Date

Kathy Holloway

ELECTION, AMENDMENT AND RESPONSE TO NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

Responsive to the Office Action, setting forth a Restriction Requirement and including a Notice to Comply with Requirements for Patent Applications Containing Nucleotide Sequence and/or Amino Acid Sequence Disclosures, mailed November 12, 1999, Applicant elects, with traverse, Group II, claims 25-39, drawn to methods of treatment of inflammatory disorders using the conjugates.

Although not set forth explicitly in the requirement, if an election of species of conjugate used in the methods is required, applicant elects the species in which the targeting agent is a chemokine and the targeted agent is a toxin. Pending claims 25-40 and 42-64 read on the elected species.

Please amend the above-captioned application as follows:

IN THE SPECIFICATION:

Please amend the specification as follows:

at page 3, line 1, replace "Baggliolini" with —Baggiolini—;

at page 6, line 21, insert —(SEQ ID NO. 93)— between "β" and ",";

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at page 13, line 13, delete "to";

at page 15, line 14, replace "use" with —used—;

at page 15, line 15, replace "This agent is a ligand-toxin conjugate" with —These agents are ligand-toxin conjugates—;

at page 27, line 4, replace "the" with —that—;

at page 31, line 20, delete "," after "Exemplary";

at page 43, line 22, replace "condons. In" with —codons. In—;

at page 58, line 12, replace "IP10" with —IP-10—;

at page 58, line 12, insert —(SEQ ID NO. 92)— between "10" and ")";

at page 58, line 29, delete "that";

at page 61, line 21, delete "of";

at page 61, line 25, replace "antiogenesis" with —angiogenesis—;

at page 65, line 17, insert —(SEQ ID NO. 90)— between "ENA-78" and ")";

at page 65, line 19, insert —(SEQ ID NO. 89)— between "NAP-2" and ")";

at page 65, line 20, insert —(SEQ ID NO. 91)— between "IP-10" and ",";

at page 65, line 21, insert —(SEQ ID NO. 92)— between "PF4" and ")";

at page 68, line 6, replace "datavbbase" with —database—;

at page 69, line 2, insert —to— between "according" and "the";

at page 73, line 4, replace "MCP-2" with —MCP-3—;

at page 84, line 7, replace "Agrwal" with —Agrawal—;

at page 84, line 10, replace "*12*" with —*17*—;

at page 84, line 13, replace "Ed" with —ed.—;

at page 86, line 9, replace "4049" with —4048—;

at page 95, line 27, delete "can be";

at page 96, line 1, replace "expressed" with —expression—;

at page 108, line 24, replace "Ed." with —ed.—;

at page 108, line 25, replace "Eds." with —eds.—;

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at page 109, line 4, insert —)— between "1986" and ".";

at page 109, line 24, replace the second "Ed." with —ed.—;

at page 132, line 4, insert —which— between "mice" and "predictably".

IN THE SEQUENCE LISTING:

Please replace the sequence listing in the above-captioned application with the attached substitute SEQUENCE LISTING into the above-captioned application. A disk copy of the SEQUENCE LISTING and verified statement also accompany this response.

IN THE CLAIMS:

Please cancel claims 1-24 and 41 without prejudice or disclaimer.

Please add claims 42-64 as follows:

—42. A method of claim 25, wherein the conjugate is selected from the group consisting of OPL98104, OPL98112, OPL98108, OPL98102, OPL98110, OPL98106, OPL98101, OPL98109, OPL98105, OPL98103, OPL98111 and OPL98107.—

—43. The method of claim 25, wherein the conjugate comprises a targeted agent and a chemokine receptor targeting agent, or a portion thereof, wherein the conjugate binds to a chemokine receptor resulting in internalization of the targeted agent in cells bearing the receptor.—

—44. The method of claim 43, wherein the conjugate comprises the following components: (chemokine receptor targeting agent)$_n$, (L)$_q$ and (targeted agent)$_m$, wherein:

L is a linker for linking the chemokine receptor targeting agent to a targeted agent;

chemokine receptor targeting agent is any moiety that selectively binds to a chemokine receptor;

m and n, which are selected independently, are at least 1; and

q is 0 or more as long as the resulting conjugate binds to the targeted receptor, is internalized and delivers the targeted agent;

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the resulting conjugate binds to a receptor that interacts with and internalizes a chemokine, whereby the targeted agent(s) is internalized in a cell bearing the receptor; and

when the conjugate contains a plurality of targeted agents the targeted agents are the same or different, and when the conjugate contains a plurality of chemokine receptor targeting agents the targeting agents are the same or different.—

—45. The method of claim 44, wherein m and n, which are selected independently, are 1-6.—

—46. The method of claim 44, wherein q is 1, n is 2 and m is 1.

—47. The method of claim 43, wherein the chemokine receptor targeting agent is a chemokine, an antibody that specifically binds to a chemokine receptor or a fragment of the chemokine or antibody, wherein the fragment binds to the receptor and internalizes the targeted agent.—

—48. The method of claim 43, wherein the chemokine receptor targeting agent specifically binds to chemokine receptors on activated leukocytes.—

—49. The method of claim 43, wherein the chemokine receptor targeting agent specifically binds to chemokine receptors on cells selected from mononuclear phagocytes (MNP), leukocytes, natural killer cells, dendritic cells, T lymphocytes and B lymphocytes.—

—50. The method of claim 49, wherein the leukocytes are selected basophils, neutrophils, eosinophils, and combinations of any two or more thereof.—

—51. The method of claim 43, wherein the targeted agent is a toxin, a nucleic acid or a therapeutic protein.

—52. The method of claim 43, wherein the chemokine receptor targeting agent and targeted agent are linked directly via a covalent or ionic linkage.—

—53. The method of claim 43, wherein the chemokine receptor targeting agent and targeting agent are joined via a linker.—

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—54. The method of claim 53, wherein the linker is a peptide linkage, a polypeptide or is chemical linker.—

—55. The method of claim 29, wherein the conjugate comprises a targeted agent and a chemokine receptor targeting agent, or a portion thereof, wherein the conjugate binds to a chemokine receptor resulting in internalization of the targeted agent in cells bearing the receptor.—

—56. The method of claim 55, wherein the conjugate comprises the following components: (chemokine receptor targeting agent)$_n$, (L)$_q$ and (targeted agent)$_m$, wherein:

L is a linker for linking the chemokine receptor targeting agent to a targeted agent;

chemokine receptor targeting agent is any moiety that selectively binds to a chemokine receptor;

m and n, which are selected independently, are at least 1; and

q is 0 or more as long as the resulting conjugate binds to the targeted receptor, is internalized and delivers the targeted agent;

the resulting conjugate binds to a receptor that interacts with and internalizes a chemokine, whereby the targeted agent(s) is internalized in a cell bearing the receptor; and

when the conjugate contains a plurality of targeted agents the targeted agents are the same or different, and when the conjugate contains a plurality of chemokine receptor targeting agents the targeting agents are the same or different.—

—57. The method of claim 55, wherein the chemokine receptor targeting agent is a chemokine, an antibody that specifically binds to a chemokine receptor or a fragment of the chemokine or antibody, wherein the fragment binds to the receptor and internalizes the targeted agent.—

—58. The method of claim 55, wherein the chemokine receptor targeting agent specifically binds to chemokine receptors on activated leukocytes.—

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—59. The method of claim 55, wherein the chemokine receptor targeting agent specifically binds to chemokine receptors on cells selected from mononuclear phagocytes (MNP), leukocytes, natural killer cells, dendritic cells, T lymphocytes and B lymphocytes.—

—60. The method of claim 59, wherein the leukocytes are selected basophils, neutrophils, eosinophils, and combinations of any two or more thereof.—

—61. The method of claim 55, wherein the targeted agent is a toxin, a nucleic acid or a therapeutic protein.

—62. The method of claim 55, wherein the chemokine receptor targeting agent and targeted agent are linked directly via a covalent or ionic linkage.—

—63. The method of claim 55, wherein the chemokine receptor targeting agent and targeting agent are joined via a linker.—

—64. The method of claim 63, wherein the linker is a peptide linkage, a polypeptide or is chemical linker.—

Please amend claims 29, 38 and 40 follows:

29. (Amended) A method for treating inflammatory responses associated with activation, proliferation and migration of immune effector cells, comprising administering a conjugate[of claim 1] to an animal mammal, whereby an inflammatory response associated with activation, proliferation migration or the immune effector cells is inhibited, wherein the conjugate comprises a targeted agent and a chemokine receptor targeting agent, or a portion thereof, wherein the conjugate binds to a chemokine receptor resulting in internalization of the targeted agent in cells bearing the receptor.

38. (Amended) A method of inhibiting proliferation, migration or activation of cells bearing chemokine receptors, comprising contacting the cells with an effective amount of a conjugate [of claim 1] that comprises a targeted agent and a chemokine receptor targeting agent, or a portion thereof, wherein

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the conjugate binds to a chemokine receptor resulting in internalization of the targeted agent in cells bearing the receptor.

39. A method of effecting gene therapy, comprising contacting cells bearing chemokine receptors with the conjugate that comprises a targeted agent and a chemokine receptor targeting agent, or a portion thereof, wherein the conjugate binds to a chemokine receptor resulting in internalization of the targeted agent in cells bearing the receptor [of claim 1], wherein the targeted agent is a nucleic acid.

REMARKS

Any fees that may be due in connection with this paper or with this application during its entire pendency may be charged to Deposit Account No. 08-1641. If a Petition for extension of time is needed, this paper is to be considered such Petition.

Claims 25-40 and 42-64 are presently pending in this application. Claims 1-24 and 41 have been cancelled without prejudice or disclaimer, and a divisional application claiming the non-elected subject matter in this case was filed on December 2, 1999 (attorney docket no. 25020-601C). Claims 29 and 38 are amended and rewritten as independent claims incorporating all limitations of cancelled base claim 1. Claims 42-64 have been added. These claims find basis, for example, in original claims 1-24. Therefore, no new matter has been added.

A substitute Sequence Listing (paper and disk copies), a DECLARATION of Stephanie Seidman regarding the addition of subject matter previously incorporated by reference, and a copy of the Notice to Comply accompany this response.

The specification has been amended to indicate entries that have been added to the Substitute Sequence Listing attached herewith, namely, SEQ ID NOS. 89-93. These sequences are incorporated by reference in the specification as originally filed. SEQ ID NOS. 89-92 are described in Clark-Lewis

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et al. (1995) *J Leukoc Biol* 57, 703-11, cited at page 2, line 20 of the specification as originally filed, and SEQ ID NO. 93 is described in Shirozu *et al.*, *Genomics, 28*: 495-500. 1995, cited at page 6, line 24 of the specification as originally filed. The specification incorporates all cited references in their entirety (see, *e.g.*, page 30, lines 1-8). Hence the added sequences do not constitute new matter. A DECLARATION of Stephanie Seidman attesting to the identify of the sequences provided in the references and included in the SEQ LISTING accompanies this response.

SEQ ID NO. 67 disclosed at page 73, line 4 of the specification was inadvertently described as the sequence of the chemokine MCP-2, instead of the chemokine MCP-3. This has been corrected. The error is evident because SEQ ID NO. 67 disclosed in the Sequence Listing as originally filed, and as filed in the Substitute Sequence Listing attached herewith, encodes amino acids identical to those set forth in Table 3 and SEQ ID NO. 22 that include the amino acid sequence of MCP-3. SEQ ID No. 21 sets forth the amino acid sequence of MCP-2. Comparison of the two reveals that SEQ ID No. 67 encodes MCP-3, not MCP-2. Therefore no new matter has been added.

All other amendments to the specification correct obvious typographical, grammatical, spelling and formatting errors. No new matter has been added.

Attached herewith is a substitute Sequence Listing, disk and paper copies, a Verified Statement that the content of the paper and computer readable copies are the same, and a copy of the Notice to Comply with Requirements for Patent Applications Containing Nucleotide Sequence and/or Amino Acid Sequence Disclosures.

The substitute Sequence Listing differs from the Sequence Listing as originally filed in that the Substitute Sequence Listing corrects the errors noted in the Raw Sequence Listing Error Report accompanying the Notice to Comply, as follows:

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at page 1, Line 17 of the Raw Sequence Listing, the base count of 43 has been changed to 49, as noted in the Notice to Comply;

at page 1, Line 20 of the Raw Sequence Listing, the base count of 82 has been changed to 88, as noted in the Notice to Comply;

at page 3, Line 97 of the Raw Sequence Listing, the duplicated line has been deleted; and

at page 4, Line 100 of the Raw Sequence Listing, the Artificial Sequence (SEQ ID NO 10) has been described as noted in item 12 on the Error Summary Sheet. SEQ ID NOS. 1-9 have been described in a similar manner.

As noted at the bottom of Page 5 of the Raw Sequence Listing, SEQ ID NO. 68, which has an amino acid Xaa in the sequence, has been explained as to the identity of Xaa, and as to the "repeat" nature of the sequence.

The substitute Sequence Listing also differs from the original in that SEQ ID NOS. 71-93 have been added to it. SEQ ID NOS. 71-88 are the amino acid sequences encoded by the nucleotide sequences corresponding to SEQ ID NOS. 52-67 and 69-70, respectively, which were in the Sequence Listing as originally filed. No new matter has been added. SEQ ID NOS. 89-93 are incorporated by reference in the specification as originally filed. Specifically, SEQ ID NOS. 89-92 are described in Clark-Lewis *et al.* (1995) *J Leukoc Biol* 57, 703-11, cited at page 2, line 20 of the specification as originally filed, and SEQ ID NO. 93 is described in Shirozu *et al.*, *Genomics*, *28*: 495-500. 1995, cited at page 6, line 24 of the specification as originally filed. Therefore, the addition of SEQ ID NOS. 89-93 to the substitute Sequence Listing does not constitute matter which goes beyond the disclosure in the application as originally filed.

The description of SEQ ID NO. 67 has been amended to read as "MCP-3" instead of "MCP-2", which was the description in the Sequence Listing as originally filed. This error is of an inadvertent and obvious nature because SEQ ID NO. 67 disclosed in the Sequence Listing as originally filed, and as filed in the substitute Sequence Listing attached herewith, is identical to amino acids set

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forth in SEQ ID No. 22 and in TABLE 3 as the sequence of MCP-3, not MCP-2, which is set forth in SEQ ID No. 21. Simple comparison of the amino acid sequences reveals that SEQ ID No. 67 encodes MCP-3, not MCP-2. Therefore, no new matter has been added.

The substitute Sequence Listing contains no new matter, or matter which goes beyond the disclosure in the application as originally filed. Accordingly, entry of the Substitute Sequence Listing into the file history of the above-captioned application is respectfully requested.

Therefore, no new matter has been added.

TRAVERSE OF THE REQUIREMENT FOR RESTRICTION

The requirement for Restriction as between groups II and III is respectfully traversed as follows.

Groups II and III

Group II is directed to methods of treatment and includes claims, such as claim 30, which, with the lanuage of the base claim included reads as follows:

30. [The method of claim 29] A method for treating inflammatory responses associated with activation, proliferation and migration of immune effector cells, comprising administering a conjugate of claim 1 to an animal mammal, whereby an inflammatory response associated with activation, proliferation migration or the immune effector cells is inhibited, **wherein the disorder or disease state comprises secondary tissue damage.**

Group III is claim 40, which reads as follows:

40. A method for treating secondary tissue damage and associated disease states, comprising administering to a subject in need thereof an effective amount of a therapeutic agent that inhibits the proliferation, migration or physiological activity of secondary tissue damage-promoting cells.

Comparison of these claims reveals that claim 30 is within the scope of claim 40. If the claims are restricted into these two groups, applicant ultimately could be granted two patents. If a patent with claim 30 issues before

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a patent, it could not be held to constitue obviousness-type double patenting cannot over an application with claim 40 in it.

See MPEP 806, paragraph 3, which states:

> [w]here inventions are related as disclosed but are not distinct as claimed, restriction is never proper. Since, if restriction is required by the Office double patenting cannot be held, it is imperative the requirement should never be made where related inventions as claimed are not distinct.

See, also MPEP 804.01, which states:

> 35 U.S.C.121, third sentence, provides that wherein the Office requires restriction, the patent of either the parent or any divisional application thereof conforming to the requirement cannot be used as a reference against the other. This apparent nullification of double patenting as ground of rejection or invalidity in such cases imposes a heavy burden on the Office to guard against erroneous requirements for restriction where the claims define essentially the same inventions in different language and which, if acquiesced in, might result in the issuance of several patents for the same invention.

Therefore reconsideration of the requirement for restriction as between groups II and III is respectfully requested.

* * *

In view of the above amendments and remarks, examination of the application on the merits is respectfully requested.

Respectfully submitted,
HELLER EHRMAN WHITE & McAULIFFE

By: _____
Stephanie L. Seidman
Registration No. 33,779

Attorney Docket No. 25020-601B
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CLIENT #:	25020-601B SLS:RH:kh
ENCLOSURES:	TRANSMITTAL LETTER (in duplicate); PRELIMINARY AMENDMENT; and RETURN POSTCARD
INVENTORS:	McDONALD et al.
SERIAL NO:	09/360,242
FILED:	JULY 22, 1999
FOR:	*METHODS AND COMPOSITIONS FOR TREATING SECONDARY TISSUE DAMAGE AND OTHER INFLAMATORY CONDITIONS AND DISORDERS*

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SERIAL NO:	09/360,242
FILED:	JULY 22, 1999
FOR:	*METHODS AND COMPOSITIONS FOR TREATING SECONDARY TISSUE DAMAGE AND OTHER INFLAMATORY CONDITIONS AND DISORDERS*

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	McDONALD et al.
Serial No.:	09/360,242
Filed:	July 22, 1999
For:	*METHODS AND COMPOSITIONS FOR TREATING SECONDARY TISSUE DAMAGE AND OTHER INFLAMMATORY CONDITIONS AND DISORDERS*
Art Unit:	1646
Examiner:	Unassigned

I hereby certify that this paper and the attached papers are being deposited with the United States Postal Service as first class mail in an envelope addressed to:

Assistant Commissioner for Patents
Washington, D.C. 20231, on this date.

10/18/99 Kathy Holloway

Date

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

Preliminary to the examination of the above-captioned application, please amend the application as follows:

IN THE SPECIFICATION:

Please amend the specification as follows:

at page 3, line 18, please replace "inhibitory" with —inflammatory—;

at page 8, line 10, please insert —(MS)— between "sclerosis" and ",";

at page 8, line 11, please insert —(AD)— between "disease" and ",";

at page 11, line 19, please replace "Probert." with "Probert";

at page 12, line 22, please replace "Baggliolini" with —Baggiolini—;

at page 13, line 25, please replace "1993a" with —1993—;

at page 16, line 20, please replace "intergers" with —integers—;

at page 17, line 9, please replace "targetd" with —targeted—;

at page 19, line 14, please replace "binds" with —bonds—;

at page 19, line 25, please replace "cytotkines" with —cytokines—;

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at page 27, line 5, please replace "incombination" with —in combination—;

at page 29, between lines 10 and 11, please insert —**(5) Summary**—;

at page 29, between lines 16 and 17, please insert —**e. Summary of linkers**—;

at page 31, line 21, please delete "IL-10";

at page 31, line 25, please replace "TRAC" with —TARC—;

at page 31, line 25, please delete "ALP";

at page 31, line 26, please delete "lungkine";

at page 34, line 23, please replace "aicd" with —acid—;

at page 35, line 29, please replace "intenalization" with "internalization";

at page 43, line 22, please replace "codons.In" with —condons. In—;

at page 46, line 8, please delete the second "other";

at page 57, line 3, please replace "exclusiviely" with —exclusively—;

at page 59, line 1, please replace "MIP-1-a" with —MIP-1-α—;

at page 61, line 23, please replace "processses" with —processes—;

at page 62, line 11, please replace "pathophyisiological" with —pathophysiological—;

at page 62, line 12, please replace "associateed" with "associated";

at page 62, line 24, please delete "(see, (2))";

at page 63, line 9, please replace "internalizaton" with —internalization—;

at page 64, line 14, please replace "Baggliolini" with —Baggiolini—;

at page 64, line 16, please replace "**Chemokine**" with —**Chemokines**—;

at page 68, line 1, please replace "Lunkine" with —Lungkine—;

at page 68, line 10, please replace ", chemokine α-5, chemokine α-6, chemokine β15 and other" with —.—;

at page 68, line 18, please delete "I. ";

at page 69, lines 4 and 12, please replace "chemotoxin" with —chemokine-fusion protein—;

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at page 69, line 16, please replace "MIP-1a" with "MIP-1α";

at page 69, line 18, please replace "MIP-1b" with —MIP-1β—;

at page 92, line 11, please replace "3'" with —3—;

at page 94, line 24, please replace "usefule" with —useful—;

at page 95, line 12, please replace "Petide" with "Peptide";

at page 97, line 3, please replace "**3**" with "**e**";

at page 104, line 25, please replace "(19820" with —(1982)—;

at page 108, line 16, please replace "al., .," with "al.,";

at page 109, lines 6 to 9, please delete "A constitutive yeast promoter such as ADH or LEU2 or an inducible promoter such as GAL may be used (. Rothstein In: *DNA Cloning Vol. 11, A Practical Approach*, Ed. DM Glover, IRL Press, Wash., D.C., 1986, Cloning in Yeast, Ch. 3).";

at page 109, line 24, please replace "Covet" with —Covey—;

at page 118, line 14, please replace "descibed" with —described—;

at page 118, line 20, please delete the second "to";

at page 119, line 11, please replace "[In Process Citation]" with —,— ;

at page 129, line 17, please replace "develope" with —develop—;

at page 131, line 7, please replace "MIP-1" with —MIP-1α)—;

at page 131, line 8, please delete "alpha)";

at page 131, lines 18 and 20, please replace "MIP-1" with —MIP-1α—;

at page 131, lines 18 and 20, please delete "alpha";

at page 137, line 2, please replace "**growth)**" with "**growth**";

at page 137, line 11, please replace "assoiciated" with "associated";

at page 137, line 23, please replace "studing" with —studying—;

at page 137, line 23, please replace "conjugtes" with —conjugates—;

at page 138, line 1, please delete the second "a";

at page 154, line 21, please replace "*seminar*" with "*Seminar*";

IN THE CLAIMS:

Please amend claims 16, 20, 23 and 33 as follows:

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16. (Amended) [T he] The conjugate of claim 14, wherein the cytokine is selected from among interleukins, lymphokines, monokines, colony-stimulating factors and receptor associated proteins.

20. (Amended) The nucleic acid of claim 19 that is DNA.

23. (Amended) A method of producing a conjugate, comprising culturing the cell of claim [21] 22 under conditions, whereby a fusion protein comprising the conjugate is expressed, and isolating the fusion protein.

33. (Amended) The method of [any of] claim 29, wherein the chemokine receptor targeting agent is a chemokine.

IN THE ABSTRACT

at page 183, line 6, please replace "neutrophiles" with —neutrophils—;

REMARKS

Any fees that may be due in connection with filing this paper, or during the entire pendency of this application, may be charged to Deposit Account No. 08-1641.

The amendments to the claims, specification and abstract correct obvious typographical errors. No new matter has been added.

FEB 22 2007

* * *

Entry of this amendment and examination of the application are respectfully requested.

Respectfully submitted,
HELLER, EHRMAN, WHITE & McAULIFFE

By: _____
Stephanie L. Seidman
Registration No. 33,779

Attorney Docket No. 25020-601B
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Client #: 25020-601B

Enclosures: SUPPLEMENTAL AMENDMENT; DECLARATION PURSUANT TO 37 C.F.R. § 1.132; and RETURN POSTCARD.

Applicant: McDonald *et al.*

Serial #: 09/360,242 **Filed:** July 22, 1999

For: *METHODS AND COMPOSITIONS FOR TREATING SECONDARY TISSUE DAMAGE AND OTHER INFLAMMATORY CONDITIONS AND DISORDERS*

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THE STAMP OF THE U.S. PATENT AND TRADEMARK OFFICE AFFIXED HERETO WILL BE EVIDENCE OF RECEIPT OF THE FOLLOWING (SENT VIA FIRST CLASS, PRIORITY MAIL) ON 09/11/00:

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Serial #: 09/360,242 **Filed:** July 22, 1999

For: *METHODS AND COMPOSITIONS FOR TREATING SECONDARY TISSUE DAMAGE AND OTHER INFLAMMATORY CONDITIONS AND DISORDERS*

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: McDONALD et al.

Serial No.: 09/360,242

Filed: July 22, 1999

For: *METHODS AND COMPOSITIONS FOR TREATING SECONDARY TISSUE DAMAGE AND OTHER INFLAMMATORY CONDITIONS AND DISORDERS*

Art Unit: 1646

Examiner: Landsman, R.

I hereby certify that this paper and the attached papers are being deposited with the United States Postal Service as first class mail in an envelope addressed to:
Assistant Commissioner for Patents,
Washington, D.C. 20231, on this date.

09/11/00
Date

Stephanie Seidman

SUPPLEMENTAL AMENDMENT

Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

Responsive to the outstanding Office Action, mailed March 2, 2000, and supplemental to the Amendment, mailed September 5, 2000, entry of the following amendments and consideration of the following remarks are respectfully requested.

IN THE SPECIFICATION:

Please amend the specification as follows:

at page 27, line 1, replace "FIGURE 1 is a schematic drawing" with —FIGURE 1A-1C presents schematic drawings—;

at page 28, line 2, after "pGEMEX-SAP", insert —(also designated herein pOPL2)—;

at page 28, line 4, replace "map of a conjugate MCP-3-AM-Shiga-A1" with — map of a plasmid, designated pOPL1, encoding the conjugate MCP-3-AM-Shiga-A1, which was—

at page 28, line 7, replace "map of a conjugate MCP-1-AM-SAP" with —map of a plasmid, designated pOPL106, encoding the conjugate MCP-1-AM-SAP—; and

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at page 28, line 8, replace "map of a conjugate MCP-3-AM-Shiga-A1" with —map of a plasmid, designated pOPL101, encoding the conjugate MCP-3-AM-Shiga-A1—.

REMARKS

This response is supplemental to the Amendment, mailed September 5, 2000 and provides the Declaration noted therein. The Amendment and remarks therein, mailed on September 5, 2000, is incorporated herein in its entirety. Any fees that may be due in connection with this paper or with this application may be charged to Deposit Account No. 50-1213. If a Petition for extension of time is needed, this paper is to be considered such Petition.

Claims 26-29, 31, 32, 35-38, 40, 42, 44-46, 48-54, 57 and 65-87 are presently pending in this application.

The DECLARATION is provided to cull evidence from the specification and to provide data that rebut the assertions made by the Office in setting forth the rejection under 35 U.S.C. §112, first paragraph, and also to show results that are not taught or suggested by the cited art.

THE DECLARATION

The DECLARATION, although not necessary to demonstrate enablement, is provided to supplement the remarks in the previous response. Much of the discussion and some of the data in the DECLARATION is also in the application.

1) It is urged that the specification provides no guidance of how to treat "every possible disorder associated with an inflammatory response."

2) It is alleged that it is "not predictable to one of skill in the art how to use a method of treating a patient with 'any' type of inflammatory response", because "Applicants do not give exact dosages or a treatment regimen."

3) Further, it is alleged that no guidance is provided, or working examples, for use of the claimed compounds in treating patients who have a disorder of the immune system, and it is not predictable to one of ordinary skill

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in the art how to treat such disorders without causing further disorders to the altered immune system.

The DECLARATION provides data that shows that the chemokine receptor targeting agent conjugates specifically target activated proliferating or migrating cells, and not quiescent cells. The DECLARATION also provides data showing that conjugates specifically target cells that express receptors to which the chemokine targeting agent binds. The DECLARATION also provides data from a mouse xenograft model showing low toxicity, in fact lower than expected, and specific targeting of tumor cells.

The DECLARATION describes explains that by targeting chemokine receptors, the conjugates are not being used to treat all or any inflammatory diseases, but to treat the inflammatory response or proliferative that accompanies or causes many disease states. Because there many chemokines and many receptors therefor and because only certain chemokine receptors are upregulated in particular conditions, it is possible to specifically and selectively target the proliferating and migrating cells that are responsible for the pathophysiological response. This type of response is shared by many diseases, including CNS trauma, arthritis, asthma, cancer cell proliferation and others (at least seventy are discussed in the specification), and particular chemokine receptors are upregulated on cells that are responsible for the disease. As taught in the specification and discussed in the DECLARATION, it is possible to select chemokine receptor targeting agents to target a particular population of cells that is proliferating or migrating in the disease state and to thereby inhibit the progression or possibly eliminate the disease. In fact, as described, it will be possible to administer a series or a combination of the conjugate to specifically target the cells that are proliferating and migrating as a disease progresses.

The DECLARATION also describes how the skilled artisan can select the appropriate targeting agent for treatment of a selected disease and how the skilled artisan can select appropriate dosages. This material is also included in

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the specification. The DECLARATION also provide evidence that immunosuppression is not an issue with these conjugates because they specifically target activated cells.

By showing the exquisite selectivity of the conjugates provided in this application, the DECLARATION also shows results not taught or suggested by the cited references, which do not mention the use of chemokine receptor-targeting agents.

* * *

In view of the above amendments and remarks, reconsideration and allowance of the application are respectfully requested.

Respectfully submitted,
HELLER EHRMAN WHITE & McAULIFFE LLP

By: _____
Stephanie Seidman
Registration No. 33,779

Attorney Docket No. 25020-601B
Address all correspondence to:
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Attorney Docket No.: 17080-002002/601B

THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: John R. McDonald et al.	Art Unit	: 1647
Serial No.	: 09/360,242	Examiner	: Robert S. Landsman
Filed	: July 22, 1999	Cust. No.	: 20985
Conf. No.	: 3887		
Title	: METHODS AND COMPOSITIONS FOR TREATING SECONDARY TISSUE DAMAGE AND OTHER INFLAMMATORY CONDITIONS AND DISORDERS		

MAIL STOP: RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

PRELIMINARY AMENDMENT AND REQUEST FOR CONTINUED EXAMINATION (RCE)

Dear Sir:

This preliminary amendment, which is responsive to the Final Office Actions, mailed April 7, 2005 and August 10, 2005, is filed with Request for Continued Examination (RCE) of the above-captioned application. Entry of the following amendments and consideration of the following remarks are respectfully requested.

Amendments to the specification begin on page 2 of this paper.

Amendments to the claims are reflected in the listing of the claims, which begin on page 3 of this paper.

Remarks/Arguments begin on page 11 of this paper.

CERTIFICATE OF MAILING BY "EXPRESS MAIL"
"Express Mail" Mailing Label Number EV738975037US
Date of Deposit: February 10, 2006
I hereby certify that this paper is being deposited with the United States Postal "Express Mail Post Office to Addressee" Service under 37 CFR §1.10 on the date indicated above and is addressed to: Commissioner for Patents, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA, 22313-1450.

Stephanie Seidman

FEB 22 2007

AMENDMENT TO THE SPECIFICATION:

Please amend the specification at page 1, under "Related Application," as lines 4-26 as follows:

This application claims the benefit of priority under 35 U.S.C. §119(e) to U.S. ~~application Serial No. 09/120,523, filed July 22, 1998, and converted to a provisional application on July 22, 1999, serial number unavailable,~~ provisional application Serial No. 60/155,185 by McDONALD, John R. and COGGINS, Philip J., entitled "METHODS AND COMPOSITIONS FOR TREATING SECONDARY TISSUE DAMAGE", filed July 22, 1998, now abandoned. This application is a ———

~~This application also claims the benefit of priority under 35 U.S.C. '120 as a~~ continuation-in-part of International PCT application No. ~~(Attorney Docket No. 25020-601PC)~~ PCT/CA99/00659, filed July 21, 1999, by Osprey Pharmaceuticals Limited, McDONALD, John R. and COGGINS, Philip J. entitled "METHODS AND COMPOSITIONS FOR TREATING SECONDARY TISSUE DAMAGE AND OTHER INFLAMMATORY CONDITIONS AND DISORDERS".

The subject matter of each of U.S. application Serial No. 09/120,523 and of International PCT application No. ~~(Attorney Docket No. 25020-601PC)~~ PCT/CA99/00659 is herein incorporated by reference in its entirety.

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AMENDMENTS TO THE CLAIMS:

Please amend claims 29, 68, 81, 72 and 89-91 as follows. This listing of claims replaces all prior versions, and listings of claims, in the application.

LISTING OF CLAIMS:

1-25. (Cancelled)

26. **(Previously Presented)** The method of claim 29, wherein the immune effector cells are leukocytes that express chemokine receptors.

27. **(Previously Presented)** The method of claim 29, wherein the inflammatory response results in secondary tissue damage.

28. **(Previously Presented)** The method of claim 29, wherein the immune effector cells are selected from mononuclear phagocytes (MNP), leukocytes, natural killer cells, dendritic cells, T lymphocytes and B lymphocytes.

29. **(Currently Amended)** A method for inhibiting ~~activation,~~ proliferation or migration of activated immune effector cells, comprising administering a conjugate to an animal, whereby ~~activation,~~ proliferation or migration of the immune effector cells is inhibited, wherein:

the conjugate comprises a targeted agent or a portion thereof and a chemokine receptor targeting agent or a portion thereof sufficient to bind to a chemokine receptor on immune effector cells and facilitate internalization of the conjugate;

the chemokine receptor targeting agent is a chemokine, an antibody that specifically binds to a chemokine receptor or a fragment of the chemokine or antibody, wherein the chemokine, antibody or fragment thereof binds to the receptor and internalizes the targeted agent in a cell;

the targeted agent or portion thereof, when internalized in a cell, alters metabolism or gene expression in the cell, regulates or alters protein synthesis in the cell, inhibits proliferation of the cell or kills the cell; and

the conjugate binds to a chemokine receptor resulting in internalization of the targeted agent in cells bearing the receptor.

30. (Cancelled)

31. **(Previously Presented)** The method of claims 29, wherein the activated, proliferating or migrating immune cells occur in a disorder or disease state that is selected from the group consisting of CNS injury, CNS inflammatory diseases, neurodegenerative disorders, heart disease, inflammatory eye diseases, inflammatory bowel diseases,

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inflammatory joint diseases, inflammatory kidney or renal diseases, inflammatory lung diseases, inflammatory nasal diseases, inflammatory thyroid diseases, inflammatory responses associated with bacterial or viral infections and cytokine-regulated cancers.

32. **(Original)** The method of claim 31, wherein the CNS inflammatory diseases and neurodegenerative disorders are selected from the group consisting of stroke, closed head injury, leukoencephalopathy, choriomeningitis, meningitis, adrenoleukodystrophy, AIDS dementia complex, Alzheimer's disease, Down's Syndrome, chronic fatigue syndrome, encephalitis, encephalomyelitis, spongiform encephalopathies, multiple sclerosis, Parkinson's disease, and spinal cord injury/trauma (SCI).

33. (Cancelled)

34. **(Previously Presented)** The method of claim 29, wherein the targeted agent is a toxin.

35. **(Previously Presented)** A method of targeted delivery of an agent into cells that express chemokine receptors, comprising associating the agent with a chemokine receptor targeting agent, whereby:

the chemokine receptor targeting agent binds to a chemokine receptor expressed on the cells; and

the agent is internalized by the cells, wherein the cells are immune effector cells.

36. **(Previously Presented)** The method of claim 35, wherein the immune effector cells are activated leukocytes.

37. **(Original)** The method of claim 27, wherein the secondary tissue damage results from spinal cord injury or trauma.

38-39. (Cancelled)

40. **(Previously Presented)** A method for inhibiting the proliferation, migration or activity of secondary tissue damage-promoting inflammatory cells, comprising administering to a subject in need thereof an effective amount of a therapeutic agent that inhibits the proliferation, migration or physiological activity of secondary tissue damage-promoting inflammatory cells, wherein the therapeutic agent is a conjugate that comprises a chemokine receptor targeting agent and a targeted agent or portion thereof selected so that conjugate binds to a chemokine receptor and internalizes the targeted agent, which inhibits the proliferation, migration or physiological activity of the secondary tissue damage-promoting cells.

41. (Cancelled)

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42. **(Previously Presented)** The method of claim 29, wherein the conjugate is selected from the group consisting of OPL98104, OPL98112, OPL98108, OPL98102, OPL98110, OPL98106, OPL98101, OPL98109, OPL98105, OPL98103, OPL98111 and OPL98107.

43. (Cancelled)

44. **(Previously Presented)** The method of claim 29, wherein the conjugate comprises the following components: (chemokine receptor targeting agent)n, (L)q and (targeted agent)m, wherein:

L is a linker for linking the chemokine receptor targeting agent to a targeted agent;

chemokine receptor targeting agent is any moiety that selectively binds to a chemokine receptor and effects internalization of the conjugate;

m and n, which are selected independently, are at least 1; and

q is 0 or more as long as the resulting conjugate binds to the targeted receptor, is internalized and delivers the targeted agent;

the resulting conjugate binds to a receptor that interacts with and internalizes a chemokine, whereby the targeted agent(s) is internalized in a cell bearing the receptor; and

when the conjugate contains a plurality of targeted agents, the targeted agents are the same or different, and when the conjugate contains a plurality of chemokine receptor targeting agents, the targeting agents are the same or different.

45. **(Previously Presented)** The method of claim 44, wherein m and n, which are selected independently, are 1-6.

46. **(Previously Presented)** The method of claim 44, wherein q is 1, n is 2 and m is 1.

47. (Cancelled)

48. **(Previously Presented)** The method of claim 44, wherein the chemokine receptor targeting agent specifically binds to chemokine receptors on activated leukocytes.

49. **(Previously Presented)** The method of claim 44, wherein the chemokine receptor targeting agent specifically binds to chemokine receptors on activated cells selected from mononuclear phagocytes (MNP), leukocytes, natural killer cells, dendritic cells, T lymphocytes and B lymphocytes.

50. **(Previously Presented)** The method of claim 49, wherein the activated leukocytes are selected from basophils, neutrophils, eosinophils or combinations of any two or more thereof.

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51. **(Previously Presented)** The method of claim 44, wherein the targeted agent is a toxin, a nucleic acid or a therapeutic protein.

52. **(Previously Presented)** The method of claim 44, wherein the chemokine receptor targeting agent and targeted agent are linked directly via a covalent or ionic linkage.

53. **(Previously Presented)** The method of claim 44, wherein the chemokine receptor targeting agent and targeted agent are joined via a linker.

54. **(Previously Presented)** The method of claim 53, wherein the linker is a peptide linkage, a polypeptide or is chemical linker.

55-56. (Cancelled)

57. **(Previously Presented)** The method of claim 44, wherein the chemokine receptor targeting agent is a chemokine or a fragment thereof that binds to the receptor and internalizes the targeted agent.

58-64. (Cancelled)

65. **(Previously Presented)** The method of claim 29, wherein the chemokine receptor targeting agent is a chemokine or a sufficient portion thereof to specifically bind to a chemokine receptor and to facilitate internalization of the conjugate.

66. **(Previously Presented)** The method of claim 29, wherein the chemokine targeting agent is a chemokine that is a member of the superfamily of chemokines that interact with at least one of the chemokine receptors selected from the group consisting of the CC-, CXC-, CX3C- and XC-receptors.

67. **(Previously Presented)** The method of claim 29, wherein the chemokine targeting agent is a chemokine that is a member of the superfamily of chemokines that interact with at least one of the chemokine receptors selected from the group consisting of the CC- and CXC- receptors.

68. **(Currently Amended))** The method of claim 65, wherein the chemokine is selected from the group consisting of IL-8, GCP-2, GRO-α, GRO-β, GRP-γ, ENA-78, PBP, CTAP III, NAP-2, LAPF-4, MIG, ~~PF4,~~ IP-10, SDF-1α, SDF-1β, SDF-2, MCP-1, MCP-2, MCP-3, MCP-4, MCP-5, MIP-1α, MIP-1β, MIP-1γ, MIP-2, MIP-2α, MIP-3α, MIP-3β, MIP-4, MIP-5, MDC, HCC-1, LD78β, eotaxin-1, eotaxin-2, I-309, SCYA17, TARC, RANTES, DC-CK-1, lymphotactin and fractalkine.

69. **(Previously Presented)** The method of claim 65, wherein the chemokine is selected from the group consisting of lungkine, ALP, Tim-1, chemokine α-5, chemokine α-6 and chemokine β15.

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70. **(Previously Presented)** The method of claim 29, wherein the chemokine receptor selected from the group consisting of CXCR-1, CXCR-2, CXCR-3, CXCR-4, CXCR-5, CCR-1, CCR-2A, CCR-2B, CCR-3, CCR-4, CCR-5, CCR-6, CCR-7, CCR-8, CCR-8, CX3CR-1, XCR1, Duffy antigen receptor for chemokines (DARC) and CD97.

71. **(Previously Presented)** The method of claim 65, wherein the chemokine receptor is selected from the group consisting of DARC, CXCR-1, CXCR-2, CXCR-3, CXCR-4, CCR-1, CCR-2A, CCR-2B, CCR-3, CCR-4, CCR-5, CCR-6, CCR-7, CCR-8, CX3CR-1, and CD97.

72. **(Currently Amended)** A method for inhibiting ~~activation,~~ proliferation or migration of activated immune effector cells, comprising contacting immune effector cells with a conjugate that comprises a targeted agent or a portion thereof and a chemokine receptor targeting agent, whereby activation~~,~~ or proliferation~~, migration~~ of the immune effector cells is inhibited, wherein:

the targeted agent or portion thereof is a toxin;

the chemokine receptor targeting agent is a chemokine or a fragment of thereof that binds to a chemokine receptor and internalizes the targeted agent; and

the conjugate binds to a chemokine receptor resulting in internalization of the targeted agent in cells bearing the receptor.

73. **(Previously Presented)** The method of claim 72, wherein the conjugate comprises the following components: (chemokine receptor targeting agent)n, (L)q and (targeted agent)m, wherein:

L is a linker for linking the chemokine or fragment thereof to a targeted agent;

m and n, which are selected independently, are at least 1; and

q is 0 or more as long as the resulting conjugate binds to the targeted receptor, is internalized and delivers the targeted agent;

the resulting conjugate binds to a receptor that interacts with and internalizes a chemokine, whereby the targeted agent(s) is internalized in a cell bearing the receptor; and

when the conjugate contains a plurality of targeted agents, the targeted agents are the same or different, and when the conjugate contains a plurality of chemokine receptor targeting agents, the targeting agents are the same or different.

74. **(Previously Presented)** The method of claim 73, wherein m and n, which are selected independently, are 1-6.

FEB 2 2 2007.

75. **(Previously Presented)** The method of claim 73, wherein q is 1, n is 2 and m is 1.

76. **(Previously Presented)** The method of claim 73, wherein the chemokine specifically binds to chemokine receptors on activated leukocytes.

77. **(Previously Presented)** The method of claim 73, wherein the chemokine specifically binds to chemokine receptors on activated cells selected from mononuclear phagocytes (MNP), leukocytes, natural killer cells, dendritic cells, T lymphocytes and B lymphocytes.

78. **(Previously Presented)** The method of claim 76, wherein the activated leukocytes are selected from basophils, neutrophils, eosinophils or combinations of any two or more thereof.

79. **(Previously Presented)** The method of claim 73, wherein the chemokine is a member of the superfamily of chemokines that interact with at least one of the chemokine receptors selected from the group consisting of the CC-, CXC-, CX3C- and XC-receptors.

80. **(Previously Presented)** The method of claim 73, wherein the chemokine is a chemokine that is a member of the superfamily of chemokines that interact with at least one of the chemokine receptors selected from the group consisting of the CC- and CXC-receptors.

81. **(Currently Amended)** The method of claim 35, wherein the chemokine is selected from the group consisting of IL-8, GCP-2, GRO-α, GRO-β, GRP-γ, ENA-78, PBP, CTAP III, NAP-2, LAPF-4, MIG, ~~PF4~~, IP-10, SDF-1α, SDF-1β, SDF-2, MCP-1, MCP-2, MCP-3, MCP-4, MCP-5, MIP-1α, MIP-1β, MIP-1γ, MIP-2, MIP-2α, MIP-3α, MIP-3β, MIP-4, MIP-5, MDC, HCC-1, LD78β, eotaxin-1, eotaxin-2, I-309, SCYA17, TARC, RANTES, DC-CK-1, lymphotactin, and fractalkine.

82. **(Previously Presented)** The method of claim 40, wherein the targeted agent, when internalized in a cell, alters metabolism or gene expression in the cell, regulates or alters protein synthesis in the cell, inhibits proliferation of the cell or kills the cell.

83. **(Previously Presented)** The method of claim 29, wherein the targeted agent is selected from among ribosome inactivating proteins (RIPs) and bacteriocins.

84. **(Previously Presented)** The method of claim 73, wherein the toxin is a ribosome inactivating protein or a toxic subunit thereof.

85. **(Previously Presented)** The method of claim 29, wherein the targeted agent is a toxin that is a ribosome inactivating protein or a toxic subunit thereof.

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86. **(Previously Presented)** A method of preparing a candidate compound for treating a disease or disorder involving activated immune cells an inflammatory response, comprising:

identifying immune cells that are activated in the disease or disorder;

identifying chemokine receptors expressed on the cells;

preparing a conjugate or plurality thereof containing toxin linked to a chemokine or a plurality of chemokines that specifically bind to the identified chemokine receptors and effect or facilitate internalization of the toxin into the cells.

87. **(Previously Presented)** The method of claim 86, wherein a plurality of conjugates that bind to a plurality of chemokine receptors are prepared.

88. **(Previously Presented)** The method of claim 29, wherein the chemokine receptor targeting agent is selected from the group consisting of IL-8, GRO-α, GRO-β, IP-10, SDF-1β, MCP-1 MCP-3, eotaxin-1, eotaxin-2 and RANTES.

89. **(Currently Amended)** The method of claim 57, wherein the chemokine receptor targeting agent is selected from the group consisting of IL-8, GCP-2, GRO-α, GRO-β, GRP-γ, ENA-78, PBP, CTAP III, NAP-2, LAPF-4, MIG, ~~PF4~~, IP-10, SDF-1α, SDF-1β, SDF-2, MCP-1, MCP-2, MCP-3, MCP-4, MCP-5, MIP-1α, MIP-1β, MIP-1γ, MIP-2, MIP-2α, MIP-3α, MIP-3β, MIP-4, MIP-5, MDC, HCC-1, LD78β, eotaxin-1, eotaxin-2, I-309, SCYA17, TARC, RANTES, DC-CK-1, lymphotactin, and fractalkine.

90. **(Currently Amended)** The method of claim 40, wherein the chemokine receptor targeting agent is selected from the group consisting of IL-8, GCP-2, GRO-α, GRO-β, GRP-γ, ENA-78, PBP, CTAP III, NAP-2, LAPF-4, MIG, ~~PF4~~, IP-10, SDF-1α, SDF-1β, SDF-2, MCP-1, MCP-2, MCP-3, MCP-4, MCP-5, MIP-1α, MIP-1β, MIP-1γ, MIP-2, MIP-2α, MIP-3α, MIP-3β, MIP-4, MIP-5, MDC, HCC-1, LD78β, eotaxin-1, eotaxin-2, I-309, SCYA17, TARC, RANTES, DC-CK-1, lymphotactin, and fractalkine.

91. **(Currently Amended)** The method of claim 86, wherein the chemokine is selected from the group consisting of IL-8, GCP-2, GRO-α, GRO-β, GRP-γ, ENA-78, PBP, CTAP III, NAP-2, LAPF-4, MIG, ~~PF4,~~ IP-10, SDF-1α, SDF-1β, SDF-2, MCP-1, MCP-2, MCP-3, MCP-4, MCP-5, MIP-1α, MIP-1β, MIP-1γ, MIP-2, MIP-2α, MIP-3α, MIP-3β, MIP-4, MIP-5, MDC, HCC-1, LD78β, eotaxin-1, eotaxin-2, I-309, SCYA17, TARC, RANTES, DC-CK-1, lymphotactin, and fractalkine.

92. **(Previously Presented)** The method of claim 29, wherein the immune effector cells are selected from among monocytes, macrophages, leukocytes and microglia.

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93. **(Previously Presented)** The method of claim 44, wherein the immune effector cells are selected from among monocytes, macrophages, leukocytes and microglia.

94. **(Previously Presented)** The method of claim 35, wherein the immune effector cells are selected from mononuclear phagocytes (MNP), leukocytes, natural killer cells, dendritic cells, T lymphocytes and B lymphocytes.

95. **(Previously Presented)** The method of claim 35, wherein the immune effector cells are selected from among monocytes, macrophages, leukocytes and microglia.

96. **(Previously Presented)** The method of claim 86, further comprising:

contacting the immune cells with the conjugate or plurality thereof, whereby the toxin is internalized.

97. **(Previously Presented)** The method of claim 96, wherein a plurality of conjugates that bind to a plurality of chemokine receptors are prepared, and the immune cells are contacted with each of the conjugates simultaneously or sequentially.

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REMARKS

Any fees that may be due in connection with the filing of this paper or with this application may be charged to Deposit Account No. 06-1050. If a Petition for Extension of time is needed, this paper is to be considered such Petition.

Claims 26-29, 31, 32, 35-37, 40, 42, 44-46, 48-54, 57 and 65-97 are pending in this application. In order to advance prosecution and reduce the number of issues for possible appeal, claims 29 and 72 are amended. Claims 68, 81 and 89-91 also are amended to delete PF4 to render them properly dependent. PF4 does not appear to specifically bind to chemokine receptors on immune effector cells..

A further DECLARATION under 37 C.F.R. §1.132 of Dr. McDonald is provided to provide a summary of the state of the art at the time of filing; to provide further evidence that depleting and/or inhibiting immune effector cells is a known method for treating diseases, conditions and disorders that have an inflammatory component; and to provide additional data that shows that conjugates prepared as described in the application have the activity described in the application in recognized models. Also provided are the following references that are cited in the DECLARATION:

Tanaka *et al.*(1996) J. Exp. Med. 184:1987-1997;
Carlos *et al.* (1994) Blood 84:2068-210;
Alon *et al.* (1994) The J. Cell Biol. 127:1485-1495;
Benveniste (1997) *J. Mol. Med. 75*:165-173;
Stout *et al.* (1997) *Frontiers in Biosciene 2*:197-206;
Makita *et al.* (1998) *Am. J. Respir. Crit. Care Med. 158*:573-579;
Kaartinen *et al.* (1995) *Arterioscler. Thromb. Vasc. Biology 15*:2047-2054;
Kaartinen *et al.* (1996) *Circulation 94*:2787-2792;
Barnes *et al.* (1998) *J. Clin. Invest.101*:2910-2919;
Qin *et al.* (1997) *J. Clin. Invest. 101*:746-754;
Ogata *et al.* (1997) *J. Pathology 182*:106-114;
Ying *et al.* (1997) *Eur. J. Immunol. 27*:3507-3516;
Gauvreau *et al.* (1997) *Am. J. Respir. Crit. Care Med. 156*:1738-1745;
Ponath *et al.* (1996) *J. Clin. Invest. 97*:604-612;
Gonazalo *et al.* (1996) *J. Clin. Invest. 98*:2332-2345;
Desbaillets *et al.* (1997) *J. Exp. Med. 186*:1201-1212;
Youngs *et al.* (1997) *Int. J. Cancer 71*:257-266;
Leek *et al.* (1997) *Cancer Res. 56*:4625-4629;
Pantoni *et al.* (1998) *Arterioscler. Thromb. Vasc. Biology 18*:503-513;
Sansores *et al.* (1997) *Ches. 112*:214-219;
Pawluczyk *et al.* (1997) *J. Am. Soc. Nephrology 8*:1525-1536;
Zoja *et al.* (1997) *J. Am. Soc. Nephrology 8*:720-729;
Lavaud *et al.* (1996) *J. Am. Soc. Nephrology 7*:2604-2615;
Rastaldi *et al.* (1996) *J. Am. Soc. Nephrology 7*:2419-2427;
Wada *et al.* (1996) *FASEB J. 10*:1418-1425;

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Hvas *et al.* (1997) *Scand. J. Immunol. 46*:195-203;
Huitinga *et al.* (1995) *Clin. Exp. Immunol. 100*:344-351;
Gerriste *et al.* (1996) *Proc. Natl. Acad. Sci. U.S.A. 93*:2499-2504;
Chiang *et al.* (1996) *J. Clin. Invest.* 97:1512-1524;
Matsumura *et al.* (1996) *J. Clin. Invest.* 97:2192-22-3;
Zwacka *et al.* (1997) *J. Clin. Invest. 100*:279-289;
Teixeira *et al.* (1997) *J. Clin. Invest. 100*:1657-1666);
Bauer *et al.* (1995) *GLIA 15*:437-446; and
Natsui et al. (1997) *J. Gastroenterol. Hepatol. 12*:801-808.

The following references, are provided to evidence that immunotoxins and cytotoxic conjugates possess the ability to bind to a targeted receptor and to internalize and also to evidence that the use of toxins is well established:

Hu *et al.* (1997) *Cellular Immunology 177*:26-34;
Mesri *et al.* (1993) *J. Biol. Chem. 268*:4853-4862;
Kreitman *et al.* (1997) *Blood 90*:252-259;
Mansfield *et al.* (1997) *Blood 90*:2020-2026;
Ogata *et al.* (1989) *Proc. Natl. Acad. Sci. U.S.A. 86*:4215-4219 (of record);
Vallera *et al.* (1997) *Protein Engineering 10*:1071-1076;
Debinski *et al.* (1995) *Clin. Cancer Res. 1*:1253-1258;
Frankel *et al.* (1996) *Protein Engineering 9*:913-919;
Chan *et al.* (1996) *Blood 88*:1445-1456; and
Batra *et al.* (1990) *J. Biol. Chem. 265*:15198-15202.

PRIORITY CLAIM

The specification is amended to insert the serial number for the converted provisional and PCT application that were unavailable at the time of filing of the application. A Request for Corrected Filing Receipt will be filed under separate cover.

THE REJECTION OF CLAIMS 26-29, 31, 32, 35-37, 40, 42, 44-46, 48-54, 57 AND 65-95 UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Claims 26-29, 31, 32, 35-37, 40, 42, 44-46, 48-54, 57 and 65-97 are rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to enable the full scope of the claims for reasons of record, which are discussed in turn below. This rejection respectfully is traversed. Consideration of the arguments of record, the Declarations of record, the Declaration presented herewith is respectfully requested.

Before addressing the issues raised in the Office Action, Applicant respectfully submits, notwithstanding the fact the individual chemokine receptor targeting agent conjugates are separately patentable, the application describes and claims a generic invention. As discussed in the previous responses and Declarations of record and in the attached Declaration, the chemokine system is intimately associated with the inflammatory response, which is mediated by immune effector cells, including leukocytes. Mediation of the immune

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response by leukocytes and other immune effector cells as described in the application was well known at the time of filing the application. The fact the chemokine receptors are upregulated on these cells was known. The application teaches that these receptors can be exploited to target the cells involved in the immune response and that by virtue of the variety of receptors and agents available it is possible to target particular cells of the immune system that are activated in particular disease states.. To achieve this, conjugates containing a chemokine receptor targeting agent, such as a chemokine, are linked to a targeted agent, such as a toxin. It is not necessary to link it only to a toxin. As described in the application, targeting to a chemokine receptor with something that binds thereto, permits internalization of any linked agent, such as a nucleic acid molecule. In this application, independent claims 29 and 72 are directed to methods for inhibiting proliferation or migration of immune effector cells; these claims recite that the agent alters metabolism or gene expression in the cell, regulates or alters protein synthesis in the cell, inhibits proliferation of the cell or kills the cell. Independent claim 40 is directed to the methods in which the immune effector cells are secondary tissue damage promoting cells. Claim 35 is directed to a method for delivering an agent into cells that express chemokine receptor; the agent is not specified. Claim 86 is directed to methods for preparing the conjugates provided in this application.

The use of the chemokine system for delivering an agent to a cell expressing a chemokine receptor is generic. Similarly, delivering a toxin to activated leukocyte will inhibit activation, proliferation and/or migration of the leukocytes and thereby attenuate the inflammatory response. These are generic approaches based upon selection of the chemokine system for targeting. The application teaches conjugates and methods for exploiting this system.

As discussed previously and discussed again in the attached Declaration, it is known that depletion or inhibition of leukocytes and other immune effector cells, attenuates the inflammatory response. It also is known that linking ligands to toxins targets the resulting conjugate to cells that express the receptor. If the receptor is one that internalizes the ligand, then the conjugate is internalized and the cells are inhibited or killed by virtue of the toxin. The toxins and uses thereof are well known in the art; the toxins are not toxic until internalized. Chemokine receptors internalize bound ligands. Hence conjugates of chemokines or other chemokine receptor targeting agents will result in internalization of the conjugate (see, *e.g.* Hu *et al.* (1997) *Cellular Immunology 177*:26-34; Mesri *et al.* (1993) *J. Biol. Chem. 268*:4853-4862; Kreitman *et al.* (1997) *Blood 90*:252-259; Mansfield *et al.*

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(1997) *Blood 90*:2020-2026; Ogata *et al.* (1989) *Proc. Natl. Acad. Sci. U.S.A. 86*:4215-4219 (of record); Vallera *et al.* (1997) *Protein Engineering 10*:1071-1076; Debinski *et al.* (1995) *Clin. Cancer Res. 1*:1253-1258; Frankel *et al.* (1996) *Protein Engineering 9*:913-919; Chan *et al.* (1996) *Blood 88*:1445-1456; and Batra *et al.* (1990) *J. Biol. Chem. 265*:15198-15202; see, also, *e.g.*, U.S. Patent No. 5,308,622, claiming methods of preventing restenosis by administering a conjugate containing basic FGF linked to a toxin; U.S. Patent No. 5,478,804 claiming methods for treating tumors with a cytotoxic conjugate that targets an FGF receptor and numerous others).

Applicant has provided data in the application and in previous Declarations and in the attached Declaration that evidence that conjugates prepared as described in the application will bind to and are internalized by cells that express the receptor for the chemokine in the application. Applicant has provided *in vitro* and *in vivo* data in animal models demonstrating this. Furthermore, Applicant has provided subsequent publications by others demonstrating targeting and internalization and toxicity of conjugate prepared by others. The attached Declaration provides data from studies using four different conjugates containing SDF-1β, MCP-1, MCP-3 and Eotaxin. The data again demonstrates that the conjugates are targeted to cells that express the receptor for the chemokine moiety in the conjugate. Hence applicant has provided data for a number of different chemokines. In addition, applicant has identified others who have prepared chemokine conjugates prepared as described in the application and demonstrated activity (Shuh *et al.* and Brühl *et al.*) For example, Shuh *et al.* shows that a conjugate containing RANTES linked to *Pseudomonas* exotoxin (PE) is effective for treatment of asthma and hence has activity. Using *in vitro* models and an *in vivo* mouse model, Shuh *et al.* demonstrates that the RANTES-PE conjugate retains the functional ability of RANTES to bind to its receptors (CCR5, CCR3 and CCR1) and internalize the linked toxin. The data in the application and in previous Declarations of record provide evidence from *in vitro* and *in vivo* models that the conjugates target the intended receptors and internalize linked agents. Cell proliferation assays and mouse xenograft models are recognized models for testing evidencing therapeutic activity of such conjugates. There is no requirement in patent law to provide clinical data. It is sufficient to provide data evidencing a therapeutic effect.

The application, as discussed previously, describes a multitude of different chemokines and provides the structures (protein sequences) thereof and also provides a variety of different toxins, whose structures and the uses thereof are well known and also are

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provided in the application. The application describes the cell types expressed in various disorders in which the inflammatory response is involved, and describes chemokine receptors expressed on such cell types. The application also describes animal models and assays for testing conjugates.

The Declaration attached hereto provides numerous references that describe the cell types involved in the inflammatory response and also chemokines expressed on the cells. A table setting forth the immune effector cells involved in particular diseases that have an inflammatory component or the involve activation, migration and/or proliferation of immune effector cells and based on a review of the literature known at or before the filing of this application (or of reviews reference such literature), is provided in the Declaration. The Declaration also states and the application teaches that the particular chemokines expressed on each cell type was known. In addition, if needed, in view of the teachings in the specification and knowledge of those of skill in the art, it would be routine to test any cell type for the expression of a chemokine receptor. Hence, the application provides a generic way to target a toxin to an immune effector cell and thereby inhibit there activation, migration and/or proliferation. Depletion or inhibition of such cells is a known approach to inhibiting or ameliorating or preventing an inflammatory response. Drugs therefor, such as corticosteroids are known to be effective and are administered for treatment a variety of disorders, including allergies, cancers, autoimmune disorders, viral infections, stroke, ischemic disorders and others. What is new in this application (in addition to the particular conjugates) is the use of chemokine receptors to deliver conjugates to the cells involved.

Declaration of Dr. McDonald

A further Declaration is provided. The Declaration provides a discussion of the inflammatory response to establish that activated immune effector cells are known to play a role in this response. The Declaration also provides evidence that those of skill in the art at the time of filing of the earliest priority application knew what types of immune cells are associated with particular diseases. The application also provides such teachings and teachings regarding the expression profiles of various chemokines. The Declaration provides further evidence that depletion/inhibition of immune effector cells is effective for mitigating inflammatory responses and for treating the consequent or associated diseases. The Declaration provides additional data for several conjugates that are exemplified in the application. Briefly the data provided in the Declaration are as follows. Four additional conjugates were demonstrated to have activity against immune effector cells, such as

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macrophage and monocytes *in vitro* and *in vivo*. The conjugates contained SDF-1, MCP-1, Eotaxin and MCP-3 and are among those exemplified in the application (see, Table 6). The SDF-1 conjugate was tested in a mouse xenograft model and shown to have activity against activated leukocytes. The tumors in treated animals were significantly smaller than those in untreated animals. Histological examination evidenced significantly less leukocyte infiltrate in the tumors of treated animals compared to controls indicating that the conjugate eradicated activated macrophage evidencing an inhibition of intratumoral blood vessel formation. As stated in the Declaration, these data corroborate previous data presented in an earlier Declaration and evidence that the SDF-1 conjugate targets CXCR4 expressing tumor, endothelial and leukocyte cells as described in the application (see, *e.g.*, Table 1).

In vitro profileration assays, demonstrate a dose response against CXCR4 expressing monocytes and and no activity against astrocytes and foreskin fibroblasts. The SDF-1 conjugate as well as the MCP-1 and MCP-3 conjugates exhibited 100% killing against highly activated proliferating THP-1 monocytes (cell line) at doses of approximately 20 µg/ml. Monocytes appear less susceptible to OPL-CXCL12-LPM (SDF-1) than T cells, which is consistent with their lower expression of the targeted receptor CXCR4.

The activity of the Eotaxin conjugate, which targets CCR3 receptor (see Table 1 in the application) was tested. Significant killing of human T cells and monocytes, which express CCR3, was observed. MCP-3 conjugate was tested against THP-1 cells and monocytes, which express CCR1, 3 and 5. MCP-3 binds to CCR1 and 3 (see Table 1 in the application) and also to CCR5. The conjugate exhibited 100% killing.

Cell proliferation assays and xenograft models are recognized assays by those of skill in the art to assess the activity of cytotoxic conjugates. As discussed previously, those of skill in the art recognize such assays (see, *e.g.*, Kreitman *et al.*, Mansfield *et al.*, Ogata *et al.* , Debinski *et al.*, and the other references cited herein and previously).

Relevant Law

The case law has been discussed in previous responses. To summarize:

Enablement is a legal determination that assesses whether a specification teaches one of skill in the art to make and use what is claimed. As noted enablement is not precluded even if some experimentation is necessary, as long as the amount of experimentation is not undue. Atlas Powder Co. v. E. I. Du Pont De Nemours Co., 750 224 USPQ 409, 3 (Fed. Cir. 1984); W. L. Gore and Associates v. Inc., 721 220 USPQ 303, 315 (Fed. Cir. 1983).

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Nothing more than objective enablement is required, and therefore it is irrelevant whether this teaching is provided through broad terminology or illustrative examples. In re Marzocchi, 439 220, 223, 169 USPQ 367, 369 (CCPA 1971). An analysis of whether the rejected claims are supported by an enabling disclosure requires a determination of whether that disclosure contained sufficient information regarding the subject matter of the claims as to teach one of skill in the art how to make and use what is claimed.

The scope of enablement is based on that which is disclosed in the specification plus the scope of what would be known to one of skill in the art without undue experimentation. *National Recovery Technologies, Inc. v. Magnetic Separation Systems, Inc.*, 166 F. 3d 1190, 49 USPQ 2d 1671 (Fed. Cir. 1999). A patent need not teach, and preferably omits, what is well known in the art. *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); and *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984). Hence all that is known to those of skill in the art is part of the disclosure of the application.

To establish a *prima facie* case of lack of enablement, the Examiner has the initial burden to establish a reasonable basis to question the enablement provided for what is claimed. In re Wright, 999 1557, 1561-62, 27 1510, 1513 (Fed. Cir. 1993). (examiner must provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure). See also Morehouse, 545 162, 192 USPQ 29 (CCPA 1976). The threshold step in resolving this issue is to determine whether the Examiner has met this burden of proof by advancing acceptable reasoning inconsistent with enablement. "Factors to be considered by the examiner in determining whether disclosure would require undue experimentation have been summarized in In re Wands, 858 731, 737, 8 1400, 1404, (Fed. Cir. 1988) and are outlined in the Guidelines. These factors include: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the claimed subject matter, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. All factors must be considered. A deficiency in meeting some factors does not preclude a finding of enablement. The Examiner only urges that it is not predictable what changes in sequence would affect activity. The claims, however, require only that the polypeptide

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possess catalytic activity; and the art establishes that proteases are tolerant of change and the specification teaches the sequence of the reference polypeptide. Consideration of a few factors is **not** dispositive.

The USPTO has released "Guidelines for Examination of Applications for Compliance with the Utility Requirement" [guidelines, which address utility under 35 U.S.C. §101 and 35 U.S.C. §112, first paragraph] and an "Overview of Legal Precedent Governing the Utility Requirement" [legal overview] to support the guidelines. Under section I.B.4. of these guidelines Examiners are reminded that:

> they must treat as true credible statements made by an applicant or a declarant in the specification or in a declaration provided under 37 CFR §1.132, unless they can show that one of ordinary skill in the art would have a rational basis to doubt the truth of such statements.

Further, the legal overview provided by the USPTO, in section II.B.1., explains that:

> [a]n applicant's assertion of utility creates a presumption of utility that will be sufficient, in most cases to satisfy the utility requirement of 35 U.S.C. §101. ..... To overcome this presumption, *the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility.* In other words, the Examiner must show that the asserted utility is not credible. [Emphasis added; see *e.g.*, *In re Langer* 503 F. 2d 1380, 183 USPQ 288 (CCPA 1974)].

The legal overview goes on to explain, in section II.B.2., when an asserted utility is not "credible":

> To assess credibility, the Examiner should determine if one of ordinary skill in the art would consider the assertions of the applicant to have any reasonable scientific basis. If they do, they should not be challenged as not being credible. Only where they do not [*e.g.*, if the assertion is "incredible in view of contemporary knowledge"], should the Examiner challenge the statement as not being credible.

Thus, the Examiner must accept as true any credible statement of utility made by the Appellant and may only challenge the statement upon a showing that those of skill in the art would consider the assertion **to have no reasonable scientific basis.**

There is no requirement that the utility of a pharmacologically active substance be proven by *in vivo* testing. In re Isaacs, 146 USPQ 193, 195 (CCPA 1965). *In vitro* tests can raise the presumption of *in vivo* utility of the claimed compounds. "A standard *in vitro* test may be sufficient to demonstrate pharmacological activity of a compound." Bigham v. Godtfredsen, 222 USPQ 632, 637 (Bd. Pat. App. & Int'f. 1984), see, also Nelson v. Bowler, 206 USPQ 881, 883 (CCPA 1980); and Cross v. Iizuka, 224 USPQ 739, 741 (Fed. Cir. 1985).

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With respect to pharmacological and therapeutic utilities, the legal overview provided by the USPTO, in section I.C., interprets Nelson v. Bowler as establishing the following:

> Knowledge of the pharmacological activity of any compound is obviously beneficial to the public. It is inherently faster and easier to combat illnesses and alleviate symptoms when the medical profession is armed with an arsenal of chemicals having known pharmacological activities. Since it is crucial to provide researchers with an incentive to disclose pharmacological activities in as many compounds as possible, we conclude that adequate proof of any such activity constitutes a showing of practical utility. ..... These general principles are equally applicable to situations where an applicant has claimed a process for treating a human or animal disorder. [Emphasis added.]

The legal overview addresses the analysis of "credibility" of such utilities, in section II.B.2., as follows:

> "Special care should be taken when assessing the credibility of an asserted therapeutic utility for a claimed invention. In such cases, a previous lack of success in treating a disease or condition, or the absence of a proven animal model for testing the effectiveness of drugs for treating a disorder in humans, should not, standing alone, serve as a basis for challenging the asserted utility under §101." (Emphasis added]

Finally, the USPTO, in its legal overview, addresses some special considerations regarding asserted therapeutic or pharmacological utilities [Section III.] stating:

> "The Federal courts have consistently reversed rejections by the Office asserting a lack of utility under §101 for inventions claiming a pharmacological or therapeutic utility where an applicant has provided evidence supporting such a utility. In view of this, Examiners should be particularly careful in their review of evidence provided in support of an asserted therapeutic or pharmacological utility."

Thus, where a credible pharmacological utility is asserted by an applicant, it must be assumed by the Examiner to be a true statement of utility unless the Examiner shows that one of skill in the art would find no rational scientific basis for the asserted utility. Further, it is important to distinguish "pharmacological activity" from "therapeutic activity". Pharmacological activity refers, essentially, to any biological activity. For example, a compound that is demonstrated, via *in vitro* or *in vivo* testing, to affect a biological function such as blood flow, hormone binding, enzyme operation, etc. *in vivo* has pharmacological activity. As described above, the court, in Nelson v. Bowler, has stated that, "Knowledge of the pharmacological activity of any compound is obviously beneficial to the public." Therefore, any pharmacological activity is practically useful.

In In re Brana 34 USPQ2d 1436, U.S. App. LEXIS 6362 (Fed. Cir. 1995) the Court has stated:

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> [A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of §112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. In re Marzocchi, 58 C.C.P.A. 1069, 439 F.2d 220, 223, 169 U.S.P.Q. (BNA) 367, 369 (WP 1971).
>
> From this it follows that the PTO has the initial burden of challenging a presumptively correct assertion of utility in the disclosure. Id. at 224, 169 U.S.P.Q. (BNA) at 370. Only after the PTO provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal evidence sufficient to convince such a person of the invention's asserted utility. See <=21> In re Bundy, 642 F.2d 430, 433, 209 U.S.P.Q. (BNA) 48, 51 (WP 1981). n17
>
> The PTO has not met this initial burden. The references cited by the Board, Pazdur and Martin, n18 do not question the usefulness of any compound as an antitumor agent or provide any other evidence to cause one of skill in the art to question the asserted utility of applicants' compounds. Rather, these references merely discuss the therapeutic predictive value of *in vivo* murine tests -- relevant only if applicants must prove the ultimate value in humans of their asserted utility. Likewise, we do not find that the nature of applicants' invention alone would cause one of skill in the art to reasonably doubt the asserted usefulness. . . .
>
> Taking these facts -- the nature of the invention and the PTO's proffered evidence -- into consideration we conclude that one skilled in the art would be without basis to reasonably doubt applicants' asserted utility on its face. The PTO thus has not satisfied its initial burden. Accordingly, applicants should not have been required to substantiate their presumptively correct disclosure to avoid a rejection under the first paragraph of § 112. In re Marzocchi, 439 F.2d at 224, 169 U.S.P.Q. (BNA) at 370.

The pending claims

The independent claims are as follows:

Claim 29 is directed to a method for inhibiting proliferation or migration of immune effector cells by administering a conjugate to an animal whereby activation, proliferation, migration of the immune effector cells is inhibited. The conjugate contains a targeted agent or a portion thereof and a chemokine receptor targeting agent or a portion thereof sufficient to bind to a chemokine receptor on immune effector cells and facilitate internalization of the conjugate; the chemokine receptor targeting agent is a chemokine, an antibody that specifically binds to a chemokine receptor or a fragment of the chemokine or antibody, wherein the chemokine, antibody or fragment thereof binds to the receptor and internalizes the targeted agent in a cell; the targeted agent or portion thereof, when internalized in a cell,

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alters metabolism or gene expression in the cell, regulates or alters protein synthesis in the cell, inhibits proliferation of the cell or kills the cell; and the conjugate binds to a chemokine receptor resulting in internalization of the targeted agent in cells bearing the receptor.

Claim 72 is directed to a method for inhibiting proliferation or migration of activated immune effector cells by contacting immune cells with a conjugate that contains a toxin or a portion thereof and a chemokine receptor targeting agent, whereby activation, proliferation, migration of the immune effector cells is inhibited. The chemokine receptor targeting agent is a chemokine or a fragment of thereof that binds to a chemokine receptor and internalizes the targeted agent; and the conjugate binds to a chemokine receptor resulting in internalization of the targeted agent in cells bearing the receptor.

Claim 35

Claim 35 is directed to a method of targeted delivery of an agent into cells that express chemokine receptors by associating the agent with a chemokine receptor targeting agent, whereby the chemokine receptor targeting agent binds to a chemokine receptor expressed on the cells; and the agent is internalized by the cells, wherein the cells are immune effector cells.

Claim 40

Claim 40 is directed to a method for inhibiting the proliferation or activity of secondary tissue damage-promoting inflammatory cells by administering an effective amount of a therapeutic agent that inhibits the proliferation, migration or physiological activity of secondary tissue damage-promoting inflammatory cells. The therapeutic agent is a conjugate that contains a chemokine receptor targeting agent and a targeted agent or portion thereof selected so that conjugate binds to a chemokine receptor and internalizes the targeted agent, which inhibits the proliferation, migration or activity of the secondary tissue damage-promoting cells.

Hence the above independent and dependent claims are not methods of treatment of particular diseases per se, but rather, are methods of targeting or inhibiting activation, proliferation or migration of immune cells that are involved in inflammatory immune responses. By virtue of targeting such cells, the inflammatory processes are altered and conditions, such as secondary tissue damage, in which such processes and cells play a role are affected and disease symptoms or manifestations are mitigated.

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Claim 86

Claim 86 is directed to a method for preparing a compound for treating a disease or disorder involving activated immune cells an inflammatory response, by:

identifying immune cells that are activated in the disease or disorder;

identifying chemokine receptors expressed on the cells;

preparing a conjugate or plurality thereof containing toxin linked to a chemokine or a plurality of chemokines that specifically bind to the identified chemokine receptors and effect or facilitate internalization of the toxin into the cells.

Dependent claims for each independent claim specify particulars regarding the conjugates and methods.

Claim 86 is directed to a methods for preparing the conjugates.

Analysis

Since the Wands factors listed above have been addressed in previous responses and they are addressed herein. In addressing them, the Examiner's arguments are rebutted in turn.

1. The Examiner states at pages 2-3 of the Office Action that

> [T]he present invention uses methods known in the art to target conjugates to activated leukocytes. Though it appears from Applicant' arguments that the claimed invention is well-known in the art, Applicant appear to be arguing that the present invention is distinct from the prior art in that the conjugates target activated leukocytes, not leukocytes in general.

It respectfully is submitted that this statement is incorrect. The instant application provides a new way to target the mediators of the inflammatory response. The new way is based on targeting chemokine receptors, which occur on immune effector cells, the cells that mediate inflammatory response.

Applicant has argued and provided evidence (see the Declaration provided herewith and prior Declarations of record) that inhibition or depletion of immune effector cells, including leukocytes, is a known approach to treating inflammatory disease. Further the application teaches that inflammation is a key element of a diverse number of systemic and multi-organ diseases. The application describes (see, *e.g.*, the Background section), the general pathology of inflammatory diseases with emphasis on CNS secondary tissue damage/diseases caused by activated leukocytes. Spinal cord injury is discussed in depth as are other conditions including traumatic brain injury, multiple sclerosis, AIDS (HIV infection), and cancers. Several non-CNS inflammatory diseases are described and

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references pertaining to treating inflammation and eradication of macrophages (which was beneficial) are described. As laid out in the Background Section, leukocytes are not necessarily the direct cause of disease (although they can be), but their pathological roles in inflammation (and by definition --- inflammation IS the action of immune cells) down the disease cascade pathway leads to an increase in disease severity, longevity and ultimately can lead to organ failure.

The immune system is an integral part of disease/trauma pathogenesis, progression and longevity to a point where organs are rendered useless. Over-zealous immune responses cause exuberant leukocyte activation, proliferation and migration to and at the site of injury/inflammation. Leukocytes are pivotal effectors of inflammatory diseases. Killing off or subduing the perpetrating leukocyte subtypes, which are a pivotal component of the pathologies in diseases, effectively mitigates the disease. Many preclinical and clinical studies have detailed that immunosuppression or leukocyte eradication decreases the severity of diseases and slows down their progression. These effector cells are high in the pathological cascades of many diseases. In the eighties Giulian *et al.* (see, *e.g.*, Giulian, D.(1987) *J. Neurosci. Res.18*:155-171; Giulian *et al.* (1993) *J. Neurosci. 13*:29-37; Giulian *et al.* (1990) *Ann. Neurol. 27*:33-42; Giulian *et al.* (1995) *Neurochem, Int. 27*:119-137; Giulian *et al.* (1989) *J. Neurosci. 9*:4416-429; Giulian *et al.* (1988) *J. Neurosci. 8*:4707-4717; Giulian *et al.* (1988) *J. Neurosci. 8*:2485-2490; Giulian *et al.* (1988) *J. Neurosci. 8*:709-714; Giulian *et al.* (1996) *J. Neurosci. 16*:3139-3153; Giulian *et al.* (1995) *J. Neurosci. 15*:7712-7726; Giulian *et al.* (1994) *Dev. Neurosci.16*:128-136; Giulian *et al.* (1993) *J. Neurosci. Res. 36*:681-693, which are of record in this application) showed that macrophage depletion was efficacious in SCI and traumatic brain injury. Indeed most of the Pharmaceutical Industry turns out drugs with different mechanisms of action to achieve immunosuppression and leukocyte death. Many lytic antibodies or antibodies fused to toxins (immunotoxins) have been used to target receptors on cells like leukocytes and cancers in order to suppress or eradicate them. This is a more all encompassing approach to therapy rather than using biological response modifiers (for example agents that neutralize specific receptors, cytokines, eicosanoids or reactive oxygen and nitrogen species). The latter only tackle one facet of disease and cannot deal out a meaningful blow. When pathological cells are eradicated there is no possibility for these cells to continue producing proinflammatory mediators and extracellular matrix proteins.

What is **new and distinct from prior approaches** is that **Applicant** has recognized that the chemokine system of receptors and ligand provides a vehicle to mitigate the

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inflammatory response. Hence Applicant is providing methods and products to achieve this goal. Applicant discloses and claims targeting chemokine receptors with conjugates that bind to the chemokine receptors and internalize the linked toxin will effectively provide a new treatment protocol for diseases and conditions that have an inflammatory component or in which the inflammatory response underlies the disease or condition.

The application and the Declarations also have established that the chemokine system provides a more regulated, versatile and elegant way to ameliorate inflammatory responses because *it provides a way to target* subtypes of cells that are specific to particular pathologies. The application describes and exemplifies this aspect in detail, listing diseases and the particular immune effector cells that participate in the disease, describing the chemokine receptor(s) expressed in the particular cells, and the chemokine that can be used to target each cell type. Prior art approaches to treating inflammatory diseases do not target the cell subtypes in the same way the this approach does. Hence, the methods and conjugates are new, but the result to be achieved (inhibition or depletion of immune effector cells involved in an inflammatory response) is not new, but is improved.

The arguments and Declarations of record and the Declaration provided herewith establish that methods of using a conjugate containing a targeting molecule and an effector molecule to target a specific receptor (on a cell such as a tumor cell) recognized by the targeting molecule is established in the art. By specifically targeting cytotoxic conjugate to a specific receptor, target cells are depleted or inhibited. The Declarations describe numerous drug therapies available to deplete or inhibit immune effector cells. As discussed above, the application establishes this as well.

The claims and application render it clear Applicant provides a way of inhibiting or depleting immune effector cells involved in pathological inflammatory responses. Those of skill in the art will recognize that the Applicant has taught use of its conjugates for mitigating inflammatory response, and thereby treating disease states associated with or caused by the inflammatory response.

The field of invention in the application states:

> The present invention relates to therapeutic compositions and their use in the **treatment of disease states.** More particularly, compounds, compositions and methods for treating disease states associated with proliferation, migration, and physiological activity of cells **involved in inflammatory responses,** including but not limited to, secondary tissue damage, are provided.

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As noted, inflammation is a key element of a diverse number of systemic and multi-organ diseases. Therefore killing activated immune effector cells achieves the goals of abolishing the migration, proliferation and hyper-inflammatory activity of targeted cells which are pivotal in the pathogenesis of inflammatory diseases. In any given inflammatory disease certain numbers of leukocytes are migrating from the periphery to the site of inflammation where they enter the tissue all under the regulation of chemokines; cells already at the site are proliferating and exerting deleterious inflammatory effects. Therefore inhibiting or abolishing all three facets of leukocyte activity is vital for disease regression. Inflammation by definition is the mobilization and activation of immune cells. It is clear therefore that *"modulation of the levels of leukocytes will interfere with and modulate a variety of pathologies"* (P3 second line of Action). This is supported by the fact that the FDA approved anti-inflammatory drug examples tabulated in Section C Of the attached Declaration Appendices 2 and 3 (and there are many more) are used in many cases for multiple indications. Immunosuppressive drugs have been employed in the treatment of inflammatory disease for over 75 years and some are still in use today despite their limitations (see, *e.g.*, review by Couser (1999) *J. Amer. Soc. Nephrol. 10*:664-665).

2. The Examiner states at page 3 of the Office Action that:

> Applicants are not claiming methods of treating any and all pathologies, but are only claiming methods of targeting activated leukocytes. While targeting activated leukocytes is not the same as claiming a method of treating diseases, the scope remains excessive. As previously argued by the Examiner, Applicants are claiming methods of using conjugates to target activated leukocytes under any conditions.

This again is a mischaracterization of the arguments of record and of the claims. Claims 29 and 72 are amended to recited that the targeted immune cells are activated immune effector cells. The application discloses a variety of pathologies, and the dependent claims recite, involving activated immune effector cells. There should be no limitation on the particular conditions for administration of the conjugate, other than the presence of the activated cells.

Claim 35 is directed to a method of targeted delivery of an agent into cells that express chemokine receptors by associating the agent with a chemokine receptor targeting agent, whereby the chemokine receptor targeting agent binds to a chemokine receptor expressed on the cells; and the agent is internalized by the cells, wherein the cells are immune effector cells. Hence, this aspect of the rejection is not pertinent to this claim.

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Similarly, the rejection is not pertinent to claim 40 or claim 86. Claim 40 is directed to a method for inhibiting the proliferation or activity of secondary tissue damage-promoting inflammatory cells by administering an effective amount of a therapeutic agent that inhibits the proliferation, migration or physiological activity of secondary tissue damage-promoting inflammatory cells. The therapeutic agent is a conjugate that contains a chemokine receptor targeting agent and a targeted agent or portion thereof selected so that conjugate binds to a chemokine receptor and internalizes the targeted agent, which inhibits the proliferation, migration or activity of the secondary tissue damage-promoting cells.

Claim 86 is directed to a method for preparing the conjugates; and involves no treatment or administration of any sort.

3. The Examiner states at pages 3-4 of the Office Action that

> Applicants have only provided minimal evidence that this targeting procedure will work. Applicants have only provided an example of three conjugates and shown that they are effective in vitro and that, at most, one is not toxic when administered in vivo. ... Furthermore, the scope and sheer magnitude of what Applicants are trying to tackle is further evident in the last paragraph on page 18 of the Response (see also paragraph 2 on page 25). ... Though Applicants continue to argue that they are not attempting to treat diseases ..., it remains that there is an incredibly vast role for leukocytes (and other immune effector cells which are not generally even discussed in the Response, adding to the sheer scope of the invention) in everything from cancer, to arthritis, to MS to trauma. This is far from an exhaustive list. Applicants argue on page 19 [of the Response] that 'the inflammatory response plays [a] role in a variety of diseases.' Though, again, Applicants have argued that they are not attempting to treat inflammation, or any disease, it is this argument regarding the role of inflammation that supports the vast scope of Applicants' invention.

In another related comment, the Examiner states at page 5 of the Office Action that

> Even, *arguendo*, Applicants are not treating diseases, the subsequent filings as discussed on pages 21-22 of the Response [filed August 10, 2004] discuss, in total, a small number of situations in which targeting immune cells may be used. Similarly, the examples in Tables 2 and 3 of the Response, in which the Examiner is only focusing on the relevant "ligand-toxin fusion proteins," are, clearly, specific ligand-toxin fusion proteins which have a specific indication. The scope of Applicants' claims is much more excessive than these subsequent data. In fact, the drugs discussed in Table 2 are for the most part only used to the potential treatment of cancers.

In another related comment, the Examiner states at the bottom of page 6 of the Office Action that:

> Given the immense role of effector cells in basically everything from maintaining homeostasis to their involvement in potentially hundreds of

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> diseases covering a broad spectrum of etiologies, it is undue experimentation for the artisan to determine the underlying cause of a particular disease with regard to the effector cell, sufficiently comprehend at which exact stage the disease is in at a given time, to identify which chemokine receptors are overexpressed, or are best targeted, while not targeting undesired cells, to monitor any changes in the leukocytes with regard to changes in chemokine receptor expression and possible function ... in order to affect any potential immune effector cell in any potential activation state in order to inhibit activation, proliferation or migration of these immune effector cell by altering metabolism or gene expression in the cell, regulating or altering protein synthesis in the cell or killing the cell.

Applicant respectfully disagrees for the reasons of record and those cited herein and will address these statements by addressing each of the Wands factors, but first will address the issues raised by the Examiner..

As stated above, and throughout the prosecution of this application, the application discloses and claims a generic invention. The Applicant has provided a modality for targeting activated immune effector cells. The Declarations of record, the Application, the Declaration submitted herewith (see *e.g.*, Table 1) and the literature in general overwhelmingly show that known specific drugs can be employed to treat inflammation as an entity and have been employed to treat a diverse variety of leukocyte-mediated human inflammatory diseases. These include: autoimmune disorders (e.g., rheumatoid arthritis, multiple sclerosis, systemic lupus erythematosus, dermatitis, psoriasis, Behcet's syndrome Sjogren's syndrome, some cancers, to name but a few). These diseases are the product of leukocyte-mediated tissue damage, which has been well documented and understood for decades (see references of record; Sakane, 1997; Matsumoto, 1996). Where diseases have a genetic foundation (e.g., cystic fibrosis, polycystic kidney disease) there is again an overzealous inflammatory response which drastically worsens the situation. Any disease or ailment that ends in "SIS" or "ITIS" is leukocyte-mediated and by definition these cells destroy tissue by several means causing organ dysfunction and disease. In several diseases leukocytes fuel disease by, for example, orchestrating angiogenesis, fibrosis and extracellular matrix breakdown (*e.g.*, in cancers for nourishment and metastasis and in arthritis for osteoclast migration and destruction of cartilage and bone). It has now been shown that macrophages transdifferentiate into osteoclasts which devour cartilage and bone in arthritis. Fibrosis includes extracellular matrix deposition and transdifferentiation of tissue resident cells (under the influence of leukocyte-derived inflammatory mediators) into, fibroblasts, myofibroblasts and pathological cells with leukocyte phenotypes. This application provides a

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new modality for targeting the inflammatory response, and compounds that specifically target groups of leukocyte types in a variety of diseases.

As discussed previously, the application teaches what receptors to target for a particular disease (*e.g.*, Table 2, Sections E, F, G), the Declaration establishes that at the time of filing of the earliest priority document the association of particular immune effector subtypes with a particular disorder was known, the application and art of record establishes that the chemokine receptor expression profiles were known, the application provides a multitude of chemokines, identifies the receptors therefore, provides working examples teaching synthesis of twelve conjugates, and testing thereof. The Declarations of record provide additional evidence of activity of these conjugates in recognized models demonstrating targeting to cells expressing the targeted receptor and killing of such cells *in vitro* and *in vivo*. There are countless examples of successful use of conjugates for targeting to cells that express targeted receptors. There is prior evidence that activity in the same type of *in vitro* proliferation assays provided in the application or prior art conjugates correlated with *in vivo* effectiveness.. Hence, armed with the knowledge of the skilled application and in view of the teachings in the specification, one of skill in the art can readily make and use the claimed conjugates to target chemokine receptors to thereby treat diseases and disorders in which migration and proliferation of activated immune effector cells play a role. The Examiner has provided no evidence that the conjugates prepared as described in the application do have the expected activities. Therefore, it respectfully is submitted that the scope of treatment of disease claimed is not excessive. As long as a disease has an inflammatory component then it becomes a target for the drugs provided in the application.

The Examiner notes that *"The scope of Applicants' invention is, again, much greater."* (than ligand-toxins and other agents given as examples in our response 8/18/04). This is true because the chemokine ligands work through chemokine receptors, which are highly regulated in health and disease. Antibodies can see multiple receptor antigens or specific antigens, which are widely distributed and at best makes such therapeutic dose low and limits their application. IL-2 for instance binds to two types of receptors, which are constitutively expressed on many cell types. Thus, for example, Ontak is limited to low doses in the treatment of terminal cancers. The instant application, as evidenced by the Declarations, shows that the chemokine system can be finely exploited to eradicate targeted receptor bearing leukocytes, cancer cells and activated endothelial cells involved in neovascularization. For example, OPL-CCL2-LPM (MCP-1-shiga fusion protein) can be

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used to treat several inflammatory diseases because the ligand/receptor (CCL2/CCR2) is pivotal in the pathology of several diseases. For example macrophages and Th1 cells that express CCR2 and respond to CCL2 (MCP-1) are a hallmark of diseases, such as multiple sclerosis, arthritis, COPD, CKD (several diseases) and SCI. Likewise OPL-CCL11-LPM/ (Eotaxin-shiga fusion protein) targets CCR3 expressing eosinophils, Th2 cells and mast cells, which are the hallmark of several allergic pulmonary, skin and nasal conditions. These drugs are selective for the pathological cells in the particular diseases because the pathological cells preferentially express the cognate receptor and because both ligands are monogamous with their receptor. The claims – *"inhibiting the activation, proliferation or migration of immune cells that are involved in the inflammatory response"* (P5 Action 1st paragraph, top) and -- I add --- by exploiting the chemokine superfamily of ligands and receptors is of reasonable scope and is commensurate with the contribution to the art.

5. Turning to a consideration of the Wand's factors (discussions from previous responses are herein incorporated by reference), it is noted that **claim 86** is completely outside the purview of the rejections. Claim 35, which is directed to targeted delivery of an agent is not discussed by the Examiner, nor is claim 40, which is directed to inhibiting the migration or proliferation of secondary tissue damaging cells. Claim 40 is of more limited scope than claims 29 and 72. Its scope and issues related thereto are not addressed by the Examiner.

(1) The breadth of the claims and the nature of the invention are discussed above and previously.

(2) The state of the prior art, the level of one of skill, and the level of predictability in the art.

As evidenced by the references provided of record and those cited herein, the art recognizes that the inflammatory response is a mediator of symptoms of diseases or conditions such as spinal cord injury, stroke, acute lung injury, acute respiratory distress syndrome, inflammatory joint diseases such as rheumatoid arthritis, HIV encephalitis, neovascularization, multiple sclerosis, spongiform encephalopathies, sepsis, ulcerative colitis, Chron's disease, proliferative vitreoretinopathy, uveitis, cancers, each of which has secondary tissue damage as part of the progression of the disease/condition.

Differences among the prior art (and even subsequent art) methods is *the choice of the system* with which to intervene. Some choose to intervene with inflammatory mediators (e.g., cytokines), others with angiogenic mediators (e.g., vascular endothelial growth factor).

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Others choose to intervene with leukocyte trafficking by exploiting the cell adhesion molecule systems (anti-selectins, anti-integrins, etc).

Numerous leukocyte depletion studies using reagents to target specific leukocyte cell-sub-populations have shown beneficial effects in a wide variety of diseases in humans and animals. General treatment strategies, such as administration of corticosteroids that target such cells and effect treatment of a wide variety of such diseases is well known. Prednisone is administered for treatment of virtually all of the listed diseases, including cancers, asthma, Chron's disease, viral infections and inflammatory disorders. The instant methods employ a different treatment modality. This clearly demonstrates that the course of seemingly unrelated diseases having the same underlying mechanism can be influenced when a specific targeting agent is administered.

As evidenced by the large body of literature directed to chemokines, one of skill in the art can readily identify and select an appropriate chemokine, or set thereof, to use based upon the teachings and guidance in the specification which teaches how to make conjugates and exemplifies how to test them for requisite activities and thereafter use them in the claimed methods. Administration of the conjugates targets chemokine receptors on immune cells, which are involved in the such conditions. The particular immune cells can be targeted by selecting a particular chemokine receptor targeting agent exactly as described in the instant application (see, for example, Table 2 and the text in the application). The activation, proliferation or migration of immune cells associated with any of the described diseases will be inhibited by administration of an appropriate conjugate to a subject as described throughout the specification.

Hence, one of skill in the art will comprehend that the methods of the instant application, which target and deliver conjugates to immune cells bearing chemokine receptors will be effective and also will influence the course of a variety of diseases by targeting the underlying mechanism. The instant methods effect treatment by targeting conjugates to the immune cells involved in the pathologies to deliver linked agents, such as toxins. The Declaration of record demonstrates this unequivocally.

Of record, the Examiner agrees with our arguments that the claims are only reciting methods of targeting activated leukocytes and do not recite treating any and all pathologies but, but maintains that the scope remains excessive. Applicant does not state that the methods described and claimed are unpredictable because they are distinct from the known methods of using conjugates and targeting leukocytes as described in the art. The skilled

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artisan has the benefit, not only of the knowledge of those of skill in the art, but also , the instant application, which teaches how to make these conjugates and how to use them. Applicant has argued the use of conjugates containing a targeting agent and a toxin to target and inhibit and deplete the targeted cells, was known in the art at the time the time the priority application was filed. The selection of the chemokine system as the a target to thereby inhibit activation, proliferation and migration of immune effector cells was not known. It was known that these cells play a role in the underlying underlying pathology of the inflammatory response and mechanism of secondary tissue damage

(3) The amount of direction provided by the application

The instant claims are directed to methods for inhibiting proliferation, migration or activation immune cells by targeting receptors expressed on such cells. As established and demonstrated above, activation, proliferation and migration of immune cells underlies inflammatory responses and secondary tissue damage. As discussed in detail, the specification provides detailed guidance for selection of a chemokine targeting agent and describes which immune cells express particular chemokine receptors.

Applicant notes that treatment of an underlying mechanism or disease/condition cannot be equated with "curing" a disease; treatment is defined in the specification as "any manner in which the symptoms of a conditions, disorder or disease are *ameliorated or otherwise beneficially altered.* Treatment also encompasses any pharmaceutical use of the compositions herein. Amelioration of the symptoms of a particular disorder by administration of a particular pharmaceutical composition refers to "any lessening, whether permanent or temporary, lasting or transient that can be attributed to or associated with administration of the composition."

As previously stated, the current claims do not recite methods of directly treating these diseases. A variety of diseases can be treated because the share an underlying common pathology driven by activated immune effector cells. This is reflected in the claims. For example, claim 31 recites:

> The method of claims 29, wherein the activated, proliferating or migrating immune cells occur in a disorder or disease state that is selected from the group consisting of CNS injury, CNS inflammatory diseases, neurodegenerative disorders, heart disease, inflammatory eye diseases, inflammatory bowel diseases, inflammatory joint diseases, inflammatory kidney or renal diseases, inflammatory lung diseases, inflammatory nasal diseases, inflammatory thyroid diseases, inflammatory responses associated with bacterial or viral infections and cytokine-regulated cancers.

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Hence the application and claims provide methods for inhibiting proliferation or migration of immune effector cells and thereby mitigating an inflammatory response and treating disorders in which such cells occur. It is noted that treatment as defined in the application is not synonymous with cure. The specification states at lines 18-26 on page 48 that:

> As used herein, treatment means any manner in which the symptoms of a conditions, disorder or disease are ameliorated or otherwise beneficially altered. Treatment also encompasses any pharmaceutical use of the compositions herein.
>
> As used herein, amelioration of the symptoms of a particular disorder by administration of a particular pharmaceutical composition refers to any lessening, whether permanent or temporary, lasting or transient that can be attributed to or associated with administration of the composition.

The specification provides a substantial amount of guidance for selecting particular chemokines for treating a particular disease and for effecting treatment thereof. For example, Table 1 in the application sets forth a list of representative chemokines associated with pathophysiological inflammatory responses, including secondary tissue damage, the receptor(s) they bind to, and the cell types affected by each in humans; Table 2 in the application sets forth a list of non-limiting exemplary chemokine-receptor targeting agents (more than a dozen) for treatment of selected diseases and conditions; Table 3 provides the amino acid sequences of a variety of chemokines; Table 5 provides physical properties of a variety of chemokine targeting agents; and Table 6 and the examples provide a dozen exemplary conjugates.

The specification also provides a detailed description of diseases and conditions associated with the inflammatory response and secondary tissue damage and provides ample guidance for the treatment of specific and classes of inflammatory disorders (see pages 151-160). The specification describes at least five broad classes of disorders, including cancer, pulmonary diseases, viral infections, secondary tissue damage, inflammatory joint diseases and autoimmune disorders, and includes a description of at least 70 diseases that fall in one or more of these categories and describes how to select a targeting agent therefor. The specification describes spinal cord injury in detail as one embodiment. As stated on described on pages 152 *et. seq.*:

It has been found herein that the cell biology of more than seventy diseases and conditions, involving most organ systems, involved pathophysiological inflammatory responses in a manner similar to the cell biology of acute SCI. The following, non-exhaustive list, and the more detailed treatment of four clinical areas, are designed to illustrate some of the more

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important similarities. Exemplary disorders and conditions, in addition to spinal cord injury, include stroke, acute lung injury and acute respiratory distress syndrome (ARDS), Alzheimer's disease, Down's syndrome, inflammatory joint disease, HIV encephalitis, growth, neovascularization (angiogenesis) and metastases of several forms of cancer including, brain, breast, and lung cancers, multiple sclerosis, spongiform encephalopathies, sepsis, ulcerative colitis and Crohn's disease, proliferative vitreoretinopathy and uveitis.

Furthermore, as demonstrated in previous responses and herein, the claims are based upon sound scientific reasoning and knowledge of those of skill in the art and are bolstered by experimental evidence that demonstrates that the underlying science is correct. One of skill in the art would recognize that the conjugates target chemokine receptors and are internalized in cells bearing such receptors. Delivery of a linked toxin will result in inhibition of such cells. As the references of record (also attached hereto) demonstrate, delivery of a toxin to a targeted cells, such as one expressing FGF, or EGF receptors is recognized to support claims to anti-tumor therapy as are the use of conjugates to bind to and inhibit immune cells.

As discussed above, targeting of inflammatory responses as a point of intervention is not new; consequently, there no need to show that all of diseases in which this response plays are role are treated/ameliorated/cured because it already is known to those of skill in the art. In addition, the use of conjugates for targeted delivery of agents, such as toxins and non-toxin agents is known; hence there is no need to prove this. The targeted delivery of agents, such as toxins to immune cells is known; hence, there should be no requirement to show that conjugates targeted to such cells function as expected. Nevertheless, the specification details how to select a chemokine targeting agent (see, e.g., Tables 2 and 3), how to prepare conjugates, and how to formulate the conjugates and administer them (see, e.g., Section F Formulation and Administration of the conjugates, page 142 *et seq.*). The conjugates are composed of molecules of known function and, as shown in the Declarations, which will function according to the activities of the components. Those of skill in the art know that conjugates will target their respective receptors, that the immune system can be targeted and modulation of immune system cells has therapeutic effect on a wide variety of diseases and conditions. This application provides a new way of modulating the immune system.

The specification clearly provides a wealth of knowledge in teaching that leukocyte-mediated diseases and conditions are diverse as arthritis, multiple sclerosis, pulmonary diseases, trauma, cancer, etc. For example, pages 66-67 of the specification describe

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chemokine receptors on secondary tissue damage-promoting cells generally belonging to the superfamily of G-coupled, seven transmembrane-domain, rhodopsin-like receptors. Table 1 illustrates a sampling of the broad range of chemokines, the receptors to which they bind, and the cell types (e.g., T lymphocytes, basophils, natural killer cells, neutrophils, dendritic cells, etc.) effected. These cell types are all leukocytes, thereby providing support for the generic term "leukocyte" in the claims. Secondary tissue damage occurs in a variety of diseases and conditions such as CNS injury, neurodegenerative disorders, heart disease, inflammatory eye diseases, cytokine-regulated cancers, etc. Examples of diseases and conditions, such as retinitis, chronic colitis, rheumatoid arthritis, IgA nephropathy, sinusitis, sarcomas, etc., that have secondary tissue damage as part of the pathology are also described. See pages 25-26, 52-61 and 69-71 of the specification.

In the present case, the specification and the state of the art are such that one of skill in the art would be capable of selecting conjugates to target leukocytes based on the disease as pointed out in Tables 2 and 3, at pages 119 et seq. and 151 et seq. Additionally, Table 2 discloses a variety of diseases/conditions and is *not* limited in scope to cancers as suggested by the Examiner. Starting at page 119, the specification describes the chemokine receptors to target for particular immune cells, which are known to be activated, migrating and/or proliferating in a number of conditions including spinal cord injury (MIP-1α, MIP-1β), traumatic brain injury (MCP-1, RANTES, MIP-1β). Starting at page 151, the specification describes which receptors and chemokines are upregulated particular disease states (i.e., IL-8, MCP-1, MCP-3, MIP-1α, RANTES and Eotaxin in inflammatory lung diseases), and in Table 2 sets forth a list of chemokines to use in conjugates and diseases to be treated therewith. *In all instances, the targeted cells are activated, proliferating or migrating immune cells.* Thus, the specification as currently written provides adequate guidance to, and teaching of, conjugates that are capable of inhibiting activation, proliferation or migration of immune effector cells by altering the metabolism or gene expression in the cell, regulating or altering protein synthesis in the cell, or killing the cell. Consequently, there is sufficient basis for altering immune mechanisms in a wide variety of conditions as disclosed in the specification.

As discussed, all of the conjugates as claim bind to chemokine receptors on activated immune cells. As described in the specification and Declaration of record, the methods in the instant application involve targeting immune cells, which express chemokine receptors. The particular chemokine receptor expressed on the cells is a function of the progress of an

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inflammatory response and also the type of disorder. The specification provides detailed guidance regarding choice of a chemokine targeting agent and the expression of chemokine receptors in various disorders and also establishes that those of skill in the art are aware of such information.

The instant claims are not directed to methods of treating the underlying pathology for treating *all* inflammatory responses, but are directed to treating the underlying pathology for treating inflammatory responses mediated by interactions between chemokines and their associated receptors by inhibiting proliferation, migration or activation immune cells by targeting chemokine receptors expressed on such cells. As established and demonstrated above, activation, proliferation and migration of immune cells underlies the inflammatory response is a variety of diseases and conditions. As discussed in detail, the specification provides detailed guidance for selection of a chemokine targeting agent and describes which immune cells express particular chemokine receptors. The specification describes the chemokine receptors to target for particular immune cells, which are known to be activated, migrating and/or proliferating in a number of conditions, including spinal cord injury (MIP-1α, MIP-1β), traumatic brain injury (MCP-1, RANTES, MIP-1β); which receptors and chemokines are up-regulated in particular disease states (i.e., IL-8, MCP-1, MCP-3, MIP-1α, RANTES and Eotaxin in inflammatory lung diseases), and Table 2 sets forth a list of examples of chemokines to use in conjugates and diseases to be treated therewith. Table 2 is reproduced herein:

TABLE 2
EXEMPLARY LIGAND(S) AND DISEASE TREATED

Ligand(s)	Disease/Condition
MCP-1 and 3, RANTES, *IP-10, IL-8, GROα*	Atherosclerosis and Restenosis
MCP-1 and 3, RANTES, *SDF-1ß*	SCI, Traumatic Brain Injury, Stroke, AD
MCP-3 and 4, RANTES, *IP-10, Mig*	Multiple Sclerosis
Eotaxin, RANTES, MDC, *SDF-1ß*	HIV
Eotaxin, MCP-1 and 4, MDC, *IL-8, ENA-78*	Inflammatory Bowel Diseases
MCP-3 and 4, RANTES, *IP-10, Mig, IL-8, ENA -78, GROα, I-TAC*	Inflammatory Joint Diseases (e.g., arthritis)
	Inflammatory Lung Diseases
MIP-1α, MIP-1ß, MCP-1, 2, 3, 4, RANTES, *IP-10, IL-8, ENA-78*	Acute lung Injuries and Fibroses
Eotaxin, MCP-4, MDC	Allergic and Eosinophil-associated Diseases

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Ligand(s)	Disease/Condition
MCP-1, *IL-8*	Inflammatory Eye Diseases
	Cancers
SDF-1ß, IP-10, Mig, IL-8, ENA-78, GROα	Glioma
MCP-1, 3, and 4, RANTES, *SDF-1ß*	Breast
MCP-1, *IL-8, ENA-78*	Lung

Italicized ligands are α or CXC chemokine family members the others are β or other chemokine family members. The ligands indicated can be used in combinations for the treatment of the indicated diseases. *In all instances, the targeted cells are activated, proliferating or migrating immune cells.*

Thus, the specification provides a description of thousands of conjugates that target chemokine receptors; describes how to prepare them and how to administer (i.e., use) them. Applicant has demonstrated throughout the specification that such conjugates target immune effector cells as claimed. See, the attached Declaration, which provides data evidencing that the conjugates target as claimed; see, also Schuh *et al.* and Brühl *et al.*. for additional *in vitro* and *in vivo evidence.*

The specification lists and provides numerous targeted agents and teaches how to make and use the conjugates. Based on the disclosure discussed of record and herein, it is unclear how and why the Examiner concludes that there is no guidance or examples in the specification as filed. The scope of the claims is not limited to what is described in a single section of the specification (e.g., the examples), but rather, the specification as a whole. MPEP § 2164.05. The application provides a more than sufficient representative number of each of the following: chemokines, a description of diseases mediated by inflammatory immune effector cells associated with the chemokines, exemplified targeted agents and all permutations and combinations of these exemplified agents. In addition to the numerous exemplifications provided, the specification also clearly teaches how to select particular chemokine targeting agents for inhibiting migration, activation or proliferation of immune effector cells, thereby treating the underlying mechanism of a variety of diseases.

The specification also provides basis for assays to determine if newly-designed conjugates (see Example 2) inhibit cell activation, proliferation, etc. Applicant submits that one skilled in the art would be performing routine experimentation to determine if the claimed conjugates were effective *in vitro* or in an *in vivo* animal model. Thus, the

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specification fully enables the use of the described conjugates to inhibit activation, proliferation or migration of the immune effector cells by altering metabolism or gene expression in the cell, regulating or altering protein synthesis in the cell, or killing the cell. This assertion is confirmed by the data and discussion as set forth in the Declaration by John McDonald. Applicant respectfully submit that the specification need not disclose *every* conjugate or test every conjugate for activity to be fully enabled for the genus of inhibitory activities claimed. MPEP § 2173.05(a). Further, when an Examiner decides that evidence submitted in a Declaration is insufficient, general statements directed to lacking validity or the evidence is not commensurate with the scope of the claims without an explanation supporting such findings is insufficient. MPEP § 716.01. The Declaration provides objective data supporting the broad disclosure in the specification and the claims. Further, the Examiner has not provided a preponderance of evidence in the form of objective evidence/references in support of the reasoning set forth in the rejection to indicate that the disclosure and data provided in the Declaration, the specification and the art, as a whole, are insufficient to enable the claims as currently recited.

As discussed below and acknowledged of record by the Examiner, the instant application discloses a generic invention, and applicant should be entitled to patent claims that cover such disclosure. The specification describes compounds and a selective treatment modality for modulating inflammatory responses (e.g., secondary tissue damage), thereby treating a variety of disorders in which an inflammatory response plays a role. The instant application teaches the use of chemokine receptors, which are expressed on immune cells, as a target for delivery of agents to immune cells. As described in previous responses and in the application, the chemokine system is intimately tied to the immune system, and specific chemokine receptors are expressed or elevated in certain diseases and disorders, in tissue damaging events, and/or during the course of development of diseases and disorders. The specification provides numerous chemokine targeting agents, identifies the association of expression of particular chemokine receptors in particular disease states or conditions and teaches how to select a chemokine targeting agent for a particular condition.

As discussed *supra*, the instant application provides detailed guidance how to make the conjugates, how to formulate them and how to administer them. The specification details the types of immune cells that are activated in a particular disease state and teaches which chemokines are expressed. The methods involve preparing the conjugates and administering them. The specification details how to make, how to formulate the conjugates and how to

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administer (i.e., use) them. The specification as noted details specifics regarding selection of a particular chemokine for a particular disease.

The specification teaches how to prepare and administer the conjugates and provides a detailed discussion of a variety of diseases and indicates which chemokine receptor targeting agent should be selected for particular diseases. Further, the instant application teaches more than the prior art, the instant applicant teaches the use of the chemokine system and chemokine receptors expressed on immune cells, such as leukocytes (and other cells) as a point of therapeutic intervention. In all instances of treatment using the instantly claimed conjugates, the targets are activated leukocytes, which are known to be involved in these diseases. The conjugates act in the same manner for each disease - they bind to the targeted immune cells and are internalized thereby. As detailed in the specification, different leukocytes are activated in different diseases, and the chemokine system can be used to target the leukocyte that will be activated in a particular disorder based on chemokine receptor expression profiles.

The application describes more than the prior art discloses; the application teaches how to make and use chemokine receptor-targeting conjugates to exploit the chemokine receptor system and to, thereby, alter migration, activation or proliferation of immune effector cells. This is a considerable advance over the art. The specification details how to do this and how to exploit the chemokine receptor system.

Further, the specification teaches how to make and use the conjugates; it describes the underlying scientific theory and describes how to select a chemokine for a particular use. The Declarations of record and the examples in the specification as acknowledged by the Examiner establish that the conjugates exhibit biological activity in recognized assays. The disclosure and data provided in the specification and in the Declarations demonstrate that the conjugates do, as described in the specification, target activated immune cells and inhibit proliferation of thereof. Once it is shown that several conjugates bind to the receptors as described, that is adequate to establish that conjugates that target chemokine receptors will bind thereto. There should be no need to show this with every different chemokine or receptor as that is not the standard for enablement. See *National Recovery Technologies, Inc. v. Magnetic Separation Systems, Inc.*, 166 F. 3d 1190, 49 USPQ 2d 1671 (Fed. Cir. 1999); and *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ 2d. 1510, 1513 (Fed. Cir. 1993). The claimed methods are directed to targeting activated immune cells. Inhibiting the proliferation of the activated immune cells (and it is known in the art that treatment modalities that inhibit

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the inflammatory response) will "treat" i.e. reduce symptoms, of any disorder that involves undesirable proliferation of activated immune cells.

From the teachings of the specification, it would be clear to one skilled in the art that the description provides sufficient basis for a generic claim. The specification goes even further to describe exemplary amino acid sequences of ligands that are useful in the claimed conjugates. The specific examples provided working examples to illustrate that the broad description. Thus, the specification sets forth multiple examples of each claim embodiment to provide basis for the genus-type language for each element and the claim as a whole is enabled as set forth in 35 U.S.C. § 112, first paragraph and the USPTO Enablement Guidelines.

(4) The existence of working examples and the quantity of experimentation

It is correct that the specification provides a generic treatment modality, it is incorrect that the application fails to provide guidance and working examples of a representative number of species falling within this generic invention. As discussed, section C of the specification provides lists of chemokine targeting agents to employ in the conjugates, their particular specificities and how to select a chemokine, the cells that express chemokine receptors and the receptors to which each chemokine binds. The specification exemplifies with working examples, preparation of 12 conjugates and details specifics regarding a variety of others see, for example, Tables 3-6, pages 25-26, 52-61, 69-71, 119 et seq., 142 et seq., 151 et seq. Example 2, all of which is supported by the Declaration. Hence, the specification provides a plethora of details and working examples. "Nothing more than objective enablement is required, and therefore it is irrelevant whether [a] teaching is provided through broad terminology or illustrative examples." *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ 2d. 1510, 1513 (Fed. Cir. 1993).

In the present case, the Declarations and subsequent art demonstrate that the conjugates have activity as described in the application; they target and bind to activated immune effector cells that express the targeted receptors, are internalized thereby, and inhibit or kill the leukocyte. As discussed above, the use of conjugates to target immune cells is known, so there is no reason to doubt that a conjugate targeted to a receptor using a targeting agent therefor will bind to the cell and act as predicted.

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The claims only require that the chemokine conjugates target immune effector cells by preparing a conjugate and administering it exactly as described in the specification. The specification provides numerous examples. Furthermore, the case law and the Patent Office Guidelines are very clear that there is no requirement in the U.S. Patent law to provide working examples nor to provide clinical data. Congress has assigned the task of protecting the public from the advertising, use and sale of harmful drugs to the Food and Drug Administration, and the Federal Trade Commission and not the U.S. Patent and Trademark Office, and it held the Patent office was wrong to insist on clinical trials. *In re Hartop*, 311 F.2d 249, 135 USPQ 419, 426-7 (CCPA 1962).

A specification is presumptively true; absent evidence of fraud, the Examiner cannot doubt the veracity of the disclosure in the specification. In *In re Brana*, 34 USPQ2d 1436, U.S. App. LEXIS 6362 (Fed. Cir. 1995), the Court stated:

> [A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. *In re Marzocchi*, 58 C.C.P.A. 1069, 439 F.2d 220, 223, 169 U.S.P.Q. (BNA) 367, 369 (WP 1971).

Any inferences regarding the presence or absence of clinical data in a specification should not be made. There is no requirement in the US Patent laws to provide any clinical data nor to include any working examples in an application. MPEP § 2164.05. Negative inferences cannot be drawn from the absence of such clinical data. Nevertheless, in this instance, the specification provides a description of thousands of conjugates, exemplifies preparation of twelve and teaches how to prepare and administer them to perform as recited in the claimed methods.

As described in the specification and supported by the Declarations, and the data in Shuh *et al.*, and Brühl *et al.*, chemokine receptors are up-regulated on cells, such as various leukocyte subtypes, that participate in such responses. Hence, the eradication or inhibition of such pathophysiologically up-regulated cells will result in amelioration of symptoms associated with secondary tissue damage and inflammatory responses mediated by interactions between chemokines and their respective receptors. As described, the chemokines and chemokine receptors constitute a large family so that the chemokine can be selected in accord

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with the teachings in the application, based upon the cell and particular receptor specifically expressed on the cell surface. The scope of enablement is that which is disclosed in the specification plus the scope of what would be known to one of skill in the art without undue experimentation. *National Recovery Technologies, Inc. v. Magnetic Separation Systems, Inc.*, 166 F. 3d 1190, 49 USPQ 2d 1671 (Fed. Cir. 1999). The specification provides exemplary lists of chemokines and identifies the cells upon which they are regulated and the disorders for which the chemokines could be used as targeting agents. In each case, the treatment modality for the recited methods is the same: one selects a chemokine receptor targeting agent based on the target cell phenotype, prepares an appropriate conjugate and administers it. The conjugate binds to the targeted receptors and is internalized thereby. If the linked agent is a toxin, the cells into which the conjugate is internalized are inhibited from migrating, proliferating or being activated. The specification details and exemplifies preparation of conjugates in great detail and the Schuh *et al.* and Brühl *et al.* references support these exemplifications. The Declarations shows that immune effector cells that express a targeted receptor are depleted. As discussed above, targeting of immune cells is not a new treatment target; the consequences of inhibiting proliferation, migration or activation of such cells are well known and documented. Those of skill in the art in light of the specification know that chemokines receptors are expressed on immune effector cells and can prepare conjugates that contain chemokine receptor targeting agents for delivery of linked agents, such as toxins and other metabolic inhibitors or other agents to such cells.

The Declaration and Examples, as well as Schuh *et al.* and Brühl *et al* and provide data demonstrating the activity of at least six different conjugates that rely on chemokines (Eotaxin, MCP-1, SDF-1β, MCP-3 and RANTES) that have very different specificity and selectivity profiles, and show that each targets and inhibits cells that express the receptor(s) for which each is specific. The Schuh *et al.* and Brühl *et al.* references demonstrate activity of RANTES-containing conjugates, which as described in the specification, targets eosinophils.

As described in the specification, and supported by the data in the Declaration, and Schuh et al. and Brühl et al. papers, targeting delivery of toxins to chemokine-bearing cells provides a means for specific targeted delivery of agents, such as toxins. The *in vitro* data and *in vivo* xenograft mouse model data of record show that the conjugates are specifically targeted to activated cells and do not interact with quiescent or non-target cells. The histological data shows that such cells are immune effector cells in the tumors.

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Furthermore, the *in vivo* data presented evidences the relatively low toxicity of the conjugates, which all are designed to target activated immune effector cells. The data provided in the Declaration shows that even high doses of OPL98111 do not completely eradicate primary human monocytes in culture, since not all of them are in the activated state. Also, a massive (non-therapeutic dose) IP dose (5 mg/kg) of OPL98111 had no apparent effect on the health of mice that were not sacrificed until over 3 weeks after treatment. Throughout the forty days of the course of experiment, mice receiving multiple doses of OPL98111 in two xenograft experiments exhibited no difference in health when compared to placebo-treated mice. Thus, there is no reason to believe that any of the conjugates to be used in the claimed methods would behave differently, since the expression profiles of chemokine receptors are well-established.

The Examiner (page 4, paragraph 3 of the Office Action) implies that the potential toxicity of the toxin moiety has not be considered. The toxins used in cytotoxic conjugates generally on not toxic unless they enter the cell; they require internalization to exhibit toxicity. This is well known. For example, the toxin moiety of the exemplified conjugates is a truncated form of the shiga A1 subunit (which in turn was previously truncated from the A2 subunit). It is enzymatic subunit of the toxin derived from Shigella dysenteriae. The truncated enzyme or toxin relies on the chemokine ligand to bind to its cognate receptor and enter cells. The free truncated toxin has no inherent functional capacity to traverse the cell membrane. Toxins, such as Ricin contain two chains, one for binding to and internalizing cells and the other that is toxic once internalized. Cytotoxic conjugates that employ ricin use the toxin chain and replace the targeting chain with the particular targeting agent of the conjugate. This is the approach used by those of skill in the art (see the reference provided herewith directed to conjugates; see the discussion in the application in section C.3). The toxins as claimed and described in the application are well known reagents.

The Declarations show inhibition of the migration and proliferation of immune effector cells in a mouse xenograft tumor model. The effect on the tumor is a consequence thereof. Thus, the conjugates act to inhibit migration or proliferation of immune effector cell as claimed. The data clearly demonstrates this, and supports the disclosure of the specification and the science and knowledge of those of skill in the art. Tumors need nourishment and secrete chemokines. Leukocyte infiltration ensues and the leukocytes provide nutrients for the tumor cells, chemoattractants for endothelial cells (angiogenesis) and more leukocytes. Therefore, macrophage (immune cell) migration and proliferation a

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part of the etiology of cancer and the data provided is pertinent. Those of skill in the art well-recognize the connection between activation of monocytes and tumor progression. Monocytes are immature macrophages and they are involved in inflammatory responses. The Declaration shows targeting and eradication of monocytes which, thereby, impedes tumorigenesis.

Thus, there is no need to employ additional models of inflammatory disease. The application and data of record demonstrate that the conjugates bind to chemokine receptors on immune effector cells and are internalized thereby and inhibit migration, proliferation or activation of immune cells or kills said immune cells; this is what is claimed. The Declaration supports this claim, and as discussed above, would be understood and accepted by those of skill in the art in view of the knowledge of those of skill in the art and the biology of the chemokine expression on immune effector cells.

The specification also teaches how to make the conjugates (and nucleic acids for fusion proteins and expression thereof) and exemplifies preparation of a dozen or more examples. The Declaration and subsequent papers of others (i.e., Schuh et al. and Brühl et al.) demonstrate that the conjugates function as claimed in *in vitro* and *in vivo* models. Thus, any remaining experimentation is *routine*.

The Examiner states at page 4 of the Office Action:

> In fact, Schuh [*sic*] teach on the left column of page 2421 that the full-length PE is toxic to most cells.
>
> Given the teachings of Schuh [*sic*], it is clear that substantial knowledge of the individual toxins must be known in order to prevent or significantly reduce any unwanted side-effects from administration of these toxins.
>
> Shuh [*sic*] et al. shows that their conjugate is only effective in Chinese Hamster Ovary cells. Shuh [*sic*] do not teach any examples of their one conjugate having any effect in vivo.

It appears that the Examiner actually is referring to Brühl *et al.* (*J. Immunol. 166*: 2420-2426 (2001)), which includes a page 2421. Comments and arguments with respect to these two statements on based the disclosure of Brühl *et al.*, which illustrates efficacy of a RANTES-PE38 conjugate *in vitro*.

Construction of conjugates containing toxins, such as *Pseudomonas* exotoxin A, or portions thereof, is a process that is well-established in the art (see, *e.g.*, Kreitman *et al.*, Debiniski *et al.*, Ogata *et al.*, Mansfield *et al.*, Mesir *et al.*, which are provided herewith).

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Brühl *et al.* states that "[s]everal fusion proteins with a truncated version of *Pseudomonas* exotoxin A have been designed. Most of them have been used to target and destroy malignant cells." *See* left column, page 2421. As early as 1975, scientists were conjugating toxins to targeting moieties such as antibodies for therapeutic purposes. See, for example, Moolten *et al.*, (*J. Natl. Cancer Inst.* 55(2): 473-477 (1975)), Theuer *et al.* (*Cancer Res.* 53: 340 (1993)), Kreitman (*Curr. Opin. Immunol.* 11(5): 570-578 (1999)), and Theuer *et al.*,. (*Am. J. Surg.* 166(3): 284-288 (1993).

Thus, the level of skill in the art is well-established (i.e., high) and unpredictability in view of the level of skill and the disclosure of the application and the knowledge of those of skill in the art and history of treatments in this area, is low. Selecting a toxin and determining what, if any, modifications are to be made toxin before conjugation would have been considered *routine* at the time the present application was filed. These toxins have been used for so many years, any particular related thereto are well known. In addition, the specification provides details for selecting and expressing toxins (see, *e.g.*, Section C.3. in the application (pages 78-90). Additionally, the specification describes synthesis of twelve conjugates (listed in Table 6) in addition to a broader description provided throughout the specification. Example 2 provides an illustration of the bioactivity of conjugates. For instance, at pages 171-174, activity of OPL98110 on activated and migrating target cells is described. An Applicant is not required to disclose every operable species to enable a genus. Nor is a working example of every operable species required to enable a genus. MPEP § 2164.03.

With respect to any side-effects, an applicant is not required to prove that the toxins do not have any unwanted side-effects or demonstrate that the invention is completely safe as asserted by the Examiner. "There is nothing in the patent statute ... which gives the Patent Office the right or the duty to require an applicant to prove that the compounds or other materials which he is claiming, and which he has stated are useful for 'pharmaceutical application' are safe, effective and reliable for use with humans." *In re Kimmel*, 292 F.2d 954, 130 USPQ 215 (CCPA 1961). Safety is not a criterion of patent statues and "absolute proof of complete safety is realistically impossible," and risk can not be equated with usefulness. *In re Anthony*, 414 F.3d 1383, 162 USPQ 594 (CCPA 1969). In *In re Hartop*, 311 F.2d 249, 135 USPQ 419, 426-7 (CCPA 1962), the Court held that Congress has assigned the task of protecting the public from the advertising, use and sale of harmful drugs to the Food and Drug Administration, and the Federal Trade Commission, not the U.S. Patent

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and Trademark Office. Furthermore, the Applicant has demonstrated (see previous Declarations of record and the attached Declaration) that the instant conjugates exhibit low toxicity

Applicant respectfully asserts that the Examiner has disregarded the teachings of Schuh *et al.*. (*Eur. J. Immunol.*, 33(11): 3080-90 (Nov. 2003)). Schuh *et al.*. teaches in the right column of the first page that the toxin cannot bind without the chemokine, and *this* binding specificity was demonstrated in Chinese hamster ovary (CHO) cells transfected with CCR5. Schuh *et al.*. additionally demonstrates *in vitro* that the conjugate *targeted and killed* CHO cells transfected with the CCR5 receptor, but not CHO cells transfected with other receptors, thereby demonstrating specificity of the chemokine to its receptor. Significantly, Schuh *et al.* also conducted ***in vivo*** testing of the conjugate in the lungs of mice as discussed in sections 2.3-2.9 and 4.2-4.8 of the article and show the effectiveness of the toxin-chemokine conjugate in an animal model.

Schuh *et al.*, describes use a mouse model of asthma, (page 4, paragraph 3). Shuh *et al.*, provides *in vivo* data as written out in the Abstract (page 3080; again in paragraph 3 on same page; page 3081; page 3084 Discussion paragraph; page 3087 Materials and Methods and throughout the document when discussing organ histology).

> *"The **intranasal** delivery of a chimeric protein comprised of RANTES/CCL5 and a truncated version of Pseudomonas exotoxin A (RANTES-PE38) significantly attenuated serum IgE, peribronchial **eosinophilia**, and airway hyperreactivity when it was administered from day 0 to 15 after intratracheal conidia challenge in A. fumigatus- sensitized **mice** but had little effect when delivered from day 15 to 30 after conidia challenge."*

Shuh *et al.* is stating that proliferation of eosinophils (culprits in allergic lug disease including asthma) as well as the production of proinflammatory IgE and hypereactivity were decreased. This evidences that chemokine-toxins act as described in the application..

With reference the Shuh *et al.*, the Examiner also states that RANTES itself is better than the conjugate in down-regulating CCR5 (page 4, paragraph 4 of the Action). This is irrelevant. Once the drug is in the cell it will be killed and unresponsive to any other stimulation via any receptor. This does not add any *"complexity to the effective treatment using the claimed methods"* at all

The Examiner argues at page 5 of the Office action that

> There is no evidence that the model used in the specification is an art-accepted model of cell toxicity *in vivo*. In addition, there appears to be no guidance or working examples that the designed conjugate, OPL98110, can inhibit cell

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migration, as claimed. Example 2 only demonstrates that the immune cells were killed once they migrated to a desired location. Furthermore, the Example only shows that the activated T-lymphocytes were affected by OPL98110. However, the claims encompass immune cells other than T-lymphocytes. In addition, the claims recite that the conjugate will inhibit the activation of these cells. However, the specification only demonstrates that the conjugates have an effect on cells which are already activated. No effect on the ability of cells which have yet to become activated is seen.

First, Applicant respectfully reminds the Examiner that the claims are not limited solely to inhibiting migration or proliferation of cells. Claim 86 is directed to a method for making conjugates; claim 40 is directed to a method for treating inhibiting proliferation or migration of cells involved in secondary tissue damage; claim 35 is directed to a method for delivering an agent into a chemokine receptor-bearing cells. Independent claim 29 recites "[a] method for inhibiting proliferation ***or*** migration of activated immune effector cells ... , wherein ... alters metabolism or gene expression in the cell, regulates or alters protein synthesis in the cell, inhibits proliferation of the cell ***or*** kills the cell." [Emphasis added.] Second, the assays used by the applicant are art-recognized. See discussion below and references provided herewith. The specification provides a cytotoxicity assay, which assay is well known for testing conjugates an demonstrate the effect of a compound on cell viability. The specification also provides as a chemotaxis assay (Example 2) and the results of testing OPL98110 in these assays. The conjugate decreased cell viability: OPL98110 was effective in inhibiting proliferation of the THP-1 cells because the THP-1 cells were killed. As taught in the specification, OPL98110 is conjugate of MCP-1 and shiga toxin. Table 1 teaches that MCP-1 binds to CCR1 and CCR2 receptors, which are present on THP-1 cells. The specification teaches the MCP-1 and monocytes are involved in the inflammatory process particularly in SCI (see, page 58). The data demonstrate that OPL98110 binds to and is internalized by the cells that it is designed to target. The data show that it is internalized in such cells. Hence, this assay, coupled with the knowledge of those of skill in the art regarding cytotoxic conjugates establishes that this conjugate performs as taught in the application. In view of the extensive experience in the art with cytotoxic conjugates for treating disease, there is no evidence of record that this conjugate (nor any claimed conjugate) will not target the intended cells and inhibit migration and/or proliferation thereof. Further, the Declaration shows that OPL98110 targets THP-1 cells, which THP-1 cells are not T-lymphocytes. THP-1 cells are human monocytes.

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The prior Declarations of record and the Declaration attached hereto provide data for additional conjugate s The Declaration attached hereto provides data evidencing activity as taught in the application for four additional conjugates The Declaration is discussed in detail above. Additionally, Brühl *et al.*,. provide an *in vitro* model and Schuh et al., as described above, provide a *working in vivo* murine model illustrating cytotoxicity of other chemokine cytotoxic conjugates.

Furthermore, the references of record and the prior art, routinely employ the proliferation assays and mouse xenograft model for testing conjugates. These are recognized models. The mice xenograft model is a recognized model that is used to assess the in vivo efficacy of agents in treating tumors. The instant Declarations show that the conjugates target activated immune effector cells in the tumors. The following list, generated in December 1994 (obtained from the Chemical Abstracts database available through Dialog), which is by no means comprehensive, of publications that describe use of this model to extrapolate from effectiveness at reducing tumor size in nude mice to in vivo effectiveness in humans:

1. Chemotherapy of childhood rhabdomyosarcomas growing as xenografts in immune-deprived mice
AUTHOR(S): Houghton, Janet A.; Houghton, Peter J.; Green, Alexander A.
JOURNAL: Cancer Res. DATE: 1982 VOLUME: 42 NUMBER: 2 PAGES: 535-9
IDENTIFIERS: neoplasm inhibitor screening model mouse, child rhabdomyosarcoma antitumor screening model
DESCRIPTORS:
Mouse...immune-deprived, human tumor graft in, as antitumor screening model

2. Antitumor activities of seventeen alkylating agents against human mammary carcinoma (MX-1) in nude mice
AUTHOR(S): Inoue, Katsuhiro; Fujimoto, Shuichi; Ogawa, Makoto
JOURNAL: Nagoya J. Med. Sci. DATE: 1981 VOLUME: 43 NUMBER: 3-4
PAGES: 89-100
IDENTIFIERS: mammary carcinoma model antitumor agent, alkylating agent breast tumor xenograft
DESCRIPTORS:
Mouse,nude...
human mammary carcinoma xenograft in, as screening model for neoplasm inhibitors
Mammary gland,neoplasm, carcinoma...
neoplasm inhibitor screening model for
Transplant and Transplantation,animal, xeno-...
of mammary carcinoma in nude mice, as screening model for neoplasm inhibitors
Neoplasm inhibitors,carcinoma...
of mammary gland, screening model for

3. Chemotherapy responsiveness of human tumors as first transplant generation xenografts in the normal mouse: six-day subrenal capsule assay
AUTHOR(S): Bogden, Arthur E.; Cobb, William R.; Lepage, Doreen J.; Haskell, Paula M.; Gulkin, Theodore A.; Ward, Allen; Kelton, Diane E.;

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Esber, Henry J.
JOURNAL: Cancer (Philadelphia) DATE: 1981 VOLUME: 48 NUMBER: 1
PAGES: 10-20
IDENTIFIERS: cancer chemotherapeutic screening model, neoplasm inhibitors screening model, breast cancer treatment model
DESCRIPTORS:
Neoplasm inhibitors...
screening model for

4. Chemotherapy of human colorectal tumor xenografts in athymic mice with clinically active drugs: 5-fluorouracil and 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU). Comparison with doxorubicin derivatives: 4'-deoxydoxorubicin and 4'-O-methyldoxorubicin
AUTHOR(S): Giuliani, Fernando C.; Zirvi, Karimullah A.; Kaplan, Nathan O.; Goldin, Abraham
JOURNAL: Int. J. Cancer DATE: 1981 VOLUME: 27 NUMBER: 1 PAGES: 5-13
IDENTIFIERS: colorectal neoplasm fluorouracil BCNU, doxorubicin deriv colorectal neoplasm, screening model anticancer drug

5. Comparison of antitumor activities of nitrosourea derivatives against mammary breast carcinoma (MX-1) in nude mice
AUTHOR(S): Inoue, Katsuhiro; Fujimoto, Shuichi; Ogawa, Makoto
JOURNAL: Gann DATE: 1980 VOLUME: 71 NUMBER: 5 PAGES: 686-91
IDENTIFIERS: nitrosourea deriv antitumor, mouse nude antitumor drug
DESCRIPTORS:
Mouse,nude...
neoplasm inhibitors evaluation in, as animal model
Neoplasm inhibitors...
nitrosoureas as, in nude mouse-human tumor xenograft system

6. An experimental model of cachexia induced by a xenografted human tumor
AUTHOR(S): Strain, Alastair J.; Easty, Gerald C.; Neville, A. Munro
JOURNAL: JNCI, J. Natl. Cancer Inst. DATE: 1980 VOLUME: 64 NUMBER: 2
PAGES: 217-21
IDENTIFIERS: cachexia cancer body water, intestine absorption cachexia cancer, nutrition cachexia cancer
DESCRIPTORS:
Neoplasm-host relationship...
cachexia pathogenesis in mouse model
Cachexia...
in cancer, mouse model for, pathogenesis of

7. Chemotherapy studies with human colon cancer xenografts in nude mice
AUTHOR(S): Osieka, R.
JOURNAL: Curr. Chemother., Proc. Int. Congr. Chemother., 10th EDITOR: Siegenthaler, Walter (Ed), Luethy, Ruedi (Ed), DATE: 1978 VOLUME: 2,
PAGES: 1149-51 PUBLISHER: Am. Soc. Microbiol.,Washington, D. C
IDENTIFIERS: colon cancer neoplasm inhibitor, mouse neoplasm inhibitor screening, animal model colon cancer
DESCRIPTORS:
Cancer,colon... nude mouse as model for
Intestine,colon,neoplasm...
nude mouse as screening model for

8. Sensitivity of a human tumor xenograft in nude (athymic) mice to various clinically-active drugs
AUTHOR(S): Ovejera, Artemio A.; Houchens, David P.; Barker, Anna D.
JOURNAL: Proc. Int. Workshop Nude Mice DATE: 1977 VOLUME: 2, PAGES:

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451-60
DESCRIPTORS:
Mouse,nude...
as animal model for cancer chemotherapy

9. Chemotherapy of human colon cancer xenografts in athymic nude mice
AUTHOR(S): Osieka, Rainhardt; Houchens, David P.; Goldin, Abraham; Johnson, Randall K.
JOURNAL: Cancer (Philadelphia) DATE: 1977 VOLUME: 40 NUMBER: 5, Suppl.
PAGES: 2640-50
DESCRIPTORS:
adenocarcinoma,neoplasm...
neoplasm inhibitors effect on, screening model for
Neoplasm inhibitors,carcinoma...
of colon, screening model for

10. Chemotherapeutic sensitivity to anticancer drugs of human tumor xenografts in athymic mice
AUTHOR(S): Ovejera, Artemio A.; Houchens, David P.; Barker, Anna D.
JOURNAL: Curr. Chemother., Proc. Int. Congr. Chemother., 10th EDITOR: Siegenthaler, Walter (Ed), Luethy, Ruedi (Ed), DATE: 1978 VOLUME: 2,
PAGES: 1144-6 CODEN: 37XLA2 LANGUAGE: English MEETING DATE: 77
PUBLISHER: Am. Soc. Microbiol.,Washington, D. C
IDENTIFIERS: neoplasm inhibitor evaluation nude mouse, animal model neoplasm inhibitor screening
DESCRIPTORS:
Neoplasm inhibitors...
evaluation of, nude mice as model for

11. Effect of serial passage in nude athymic mice on the growth characteristics and chemotherapy responsiveness of 13762 and R3230AC mammary tumor xenografts
AUTHOR(S): Bogden, Arthur E.; Kelton, Diane E.; Cobb, William R.; Gulkin, Theodore A.; Johnson, Randall K.
JOURNAL: Cancer Res. DATE: 1978 VOLUME: 38 NUMBER: 1 PAGES: 59-64
IDENTIFIERS: neoplasm inhibitor screening model, mouse athymic neoplasm inhibitor screening
DESCRIPTORS:
Mouse,nude athymic...
as neoplasm inhibitor screening model, serial passage of tumor effecton
Neoplasm inhibitors...
screening of, nude athymic mouse as model for, serial passage of tumor effect on

12. Chemotherapy of human tumor xenografts in genetically athymic mice
AUTHOR(S): Ovejera, Artemio A.; Houchens, David P.; Barker, Anna D.
JOURNAL: Ann. Clin. Lab. Sci. DATE: 1978 VOLUME: 8 NUMBER: 1 PAGES:50-6
IDENTIFIERS: neoplasm inhibitor screening model, mouse athymic antitumor screening
DESCRIPTORS:
Mouse,athymic...
in neoplasm inhibitor screening

13. Comparative evaluation of the effectiveness of anticancer drugs against human lung cancer xenografts growing in mice in diffusion chambers
AUTHOR(S): Krutova, T. V.; Korman, D. B.; Potapov, Yu. N.; Pashkova, V. S.

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JOURNAL: Izv. Akad. Nauk SSSR, Ser. Biol. DATE: 1984 NUMBER: 6 PAGES:901-8 Neoplasm inhibitors...
screening of, human xenograft model for

14. Screening test of antitumor agents by human tumor cell lines in nude mice in ascitic form
AUTHOR(S): Kitahara, Takeshi; Minato, Keisuke; Shimoyama, Masanori
JOURNAL: Gan no Rinsho DATE: 1984 VOLUME: 30 NUMBER: 9 PAGES: 1158-67
DESCRIPTORS:
Mouse,nude...
model, for screening of antitumor agents

15. Characterization of a xenograft model of human ovarian carcinoma which produces ascites and intraabdominal carcinomatosis in mice
AUTHOR(S): Hamilton, Thomas C.; Young, Robert C.; Louie, Karen G.; Behrens, Brent C.; McKoy, Wilma M.; Grotzinger, Karen R.; Ozols, Robert F.
JOURNAL: Cancer Res. DATE: 1984 VOLUME: 44 NUMBER: 11 PAGES: 5286-90
DESCRIPTORS:
Antigens,CA 125...
expression of, by human ovarian carcinoma model in nude mice
Receptors...
for hormones, of human ovarian cancer model in nude mice
Ovary,carcinoma,neoplasm...
model of human, hormone receptors and growth characteristics of, in nude mice, treatment in relation to
Carcinoma...
model of ovarian human, hormone receptors and growth characteristics of, in nude mice, treatment in relation to
Transplant and Transplantation,animal...
of ovarian carcinoma of human, hormone receptors and growth characteristics of, in nude mice
Antigens... Estrogens... Hormones...
receptors for, of human ovarian carcinoma model in nude mice

16. Chemosensitivity of human gastrointestinal and breast cancer xenografts in nude mice and predictability to clinical response of anticancer agents
AUTHOR(S): Fujita, M.; Fujita, F.; Taguchi, T.
JOURNAL: Immune-Defic. Anim., Int. Workshop Immune-Defic. Anim. Exp. Res., 4th EDITOR: Sordat, Bernard (Ed), DATE: 1984 PAGES: 311-15
MEETING DATE: 820000 PUBLISHER: Karger, Basel, Switz
IDENTIFIERS: antitumor screening human xenograft mouse
DESCRIPTORS:
Digestive tract,neoplasm...
chemosensitivity of, in human xenograft-nude mouse model
Mouse,nude... human tumors xenografted into, for antitumor screening

17. Growth pattern of tumor xenografts in Wistar rats after treatment with cyclophosphamide, total lymphoid irradiation and/or cyclosporin A
AUTHOR(S): Hoogenhout, J.; Kazem, I.; Jerusalem, C. R.; Bakkeren, J. A. J.; De Jong, J.; Kal, H. B.; Van Munster, P. J. J.
JOURNAL: Int. J. Radiat. Oncol., Biol. Phys. DATE: 1983 VOLUME: 9
NUMBER: 6 PAGES: 871-9
IDENTIFIERS: tumor xenograft growth rat model, immunosuppression tumor growth rat model
DESCRIPTORS:
Neoplasm inhibitors...
immunosuppressed rats with human and mouse xenografts for evaluation of Radiotherapy...

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immunosuppression from cyclophsophamide and cyclosporin A and, human and rat tumor xenograft growth response to, in rat model
Rat...
tumor xenografts of human and mouse in immunosuppressed, for neoplasm growth and neoplasm inhibitors evaluation

18. Human brain tumor xenografts in nude mice as a chemotherapy model
AUTHOR(S): Houchens, David P.; Ovejera, Artemio A.; Riblet, Sylva M.; Slagel, Donald E.
JOURNAL: Eur. J. Cancer Clin. Oncol. DATE: 1983 VOLUME: 19 NUMBER: 6
PAGES: 799-805
IDENTIFIERS: brain tumor xenograft chemotherapy model
DESCRIPTORS:
Neoplasm...
of brain of human, nude mouse xenograft of, as chemotherapy model

19. Evaluation of the response of a panel of human melanoma tissue-cultured cell lines xenografted in nude mice to four anticancer drugs of known clinical activity
AUTHOR(S): Bellet, Robert E.; Danna, Victoria; Mastrangelo, Michael J.; Eaton, Gordon J.; Berd, David
JOURNAL: Proc. Int. Workshop Nude Mice DATE: 1982 VOLUME: 3rd NUMBER: Vol. 2 PAGES: 649-56
IDENTIFIERS: anticancer screening nude mouse model
DESCRIPTORS:
Mouse,nude...
human melanoma tissue-cultured cell line xenografted in, as anticancer screening model

20. New method for evaluating the effect of experimental chemotherapy on human xenografts in nude mice: use of lactate dehydrogenase isozyme
AUTHOR(S): Hayata, Satoshi; Fujita, Masahide; Nakano, Yosuke; Kumagai, Michihiko; Hakozaki, Michinori; Taguchi, Tetsuo
JOURNAL: Curr. Chemother. Immunother., Proc. Int. Congr. Chemother., 12th
EDITOR: Periti, Piero (Ed), Gialdroni Grassi, Giuliana (Ed), DATE: 1982
VOLUME: 2, PAGES: 1283-4 MEETING DATE: 810000 PUBLISHER: Am. Soc. Microbiol.,Washington, D. C
IDENTIFIERS: chemotherapy evaluation model, lactate dehydrogenase chemotherapy evaluation
DESCRIPTORS:
Neoplasm inhibitors...
model for evaluation of, neoplasms of humans xenografts in, lactate dehydrogenase detn. in relation to

21. Use of the nude mouse-human cancer xenograft system for testing sensitivity to anticancer drugs
AUTHOR(S): Fujita, Masahide; Taguchi, Tetsuo
JOURNAL: Gan to Kagaku Ryoho DATE: 1982 VOLUME: 9 NUMBER: 4 PAGES: 606-15
IDENTIFIERS: antitumor drug screen graft model, mouse cancer graft antitumor screen
DESCRIPTORS:
Neoplasm...
grafts of human, in nude mouse, as system for neoplasm inhibitors screening

22. Combined modality treatment using radiation and/or chemotherapy in an athymic nude mouse-human medulloblastoma and glioblastoma xenograft model

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AUTHOR(S): Slagel, Donald E.; Feola, Jose; Houchens, David P.; Ovejera, Artemio A.
JOURNAL: Cancer Res. DATE: 1982 VOLUME: 42 NUMBER: 3 PAGES: 812-16
IDENTIFIERS: brain tumor chemotherapy radiotherapy, nude mouse brain tumor therapy
DESCRIPTORS:
Brain,neoplasm... Neoplasm...
chemotherapy and radiotherapy of, human tumors in nude mouse as model for

23. Comparison of the chemosensitivity between clinical specimens and their xenografts in nude mice by SDI test and the predictive value of in vivo chemosensitivity test using nude mice
AUTHOR(S): Sakamoto, Yasuo; Fujita, Masahide; Goi, Mamiyo; Tsukamoto, Fumine; Sugimoto, Takuji; Okuyama, Yasushi; Rhi, Minehide; Kusuyama, Takatsugu; Fujita, Fumiko
JOURNAL: Gan to Kagaku Ryoho DATE: 1993 VOLUME: 20 NUMBER: 4 PAGES: 447-54 CODEN: GTKRDX ISSN: 0385-0684 LANGUAGE: Japanese
IDENTIFIERS: antitumor chemosensitivity succinate dehydrogenase inhibition
DESCRIPTORS:
Neoplasm inhibitors...
chemosensitivity test for, using succinate dehydrogenase inhibition, in clin. specimens and nude mouse model
9002-02-2 anticancer drugs chemosensitivity test using inhibition of, in clin. specimens and nude mouse model

24. Evaluation of metastatic human tumor burden and response to therapy in a nude mouse xenograft model using a molecular probe for repetitive human DNA sequences
AUTHOR(S): Shoemaker, Robert H.; Smythe, Anne M.; Wu, Lin; Balaschak, Michael S.; Boyd, Michael R.
JOURNAL: Cancer Res. DATE: 1992 VOLUME: 52 NUMBER: 10 PAGES: 2791-6
IDENTIFIERS: nude mouse model human tumor metastasis, hybridization repetitive DNA probe
DESCRIPTORS:
Nucleic acid hybridization,DNA-DNA, dot-blot...
human repetitive DNA probes in, for anal. of human tumor metastasis in nude mice models

25. Toxicity of anticancer agents, growth and chemosensitivity of human tumor xenografts in a segregating stock of AF nude mice
AUTHOR(S): Maruo, Kohji; Emura, Reiko; Ohnishi, Yasuyuki; Endo, Sachio; Ueyama, Yoshito; Nomura, Tatsuji
JOURNAL: Lab. Anim. DATE: 1991 VOLUME: 25 NUMBER: 4 PAGES: 342-7
IDENTIFIERS: antitumor screening mouse model

The above sampling of publications clearly establishes that the rodent xenograft model is a recognized model for predicting the efficacy of therapeutics.

Furthermore, cancers are exemplary of diseases that include an underlying inflammatory component. Cancers can be viewed as inflammatory diseases even when the cells are not of hematologic origin. Cancer cells display many of the phenotypes ascribed to leukocyte subgroups and by definition can be regarded as inflammatory cells. They have the capacity to secrete proteases and proinflammatory mediators (including chemokines) and to

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perform phagocytosis. In addition cancer cells express various receptors including cytokine, chemokine, and growth factor receptors; cell adhesion molecules and metalloproteinases to facilitate metastasis; and undergo transdifferentiation (as do leukocytes). As an example of the latter, colon carcinoma cells undergo epithelial-mesenchymal transition with the concomitant increase in expression of CXCR1 and CXCL8 and thus enhance motility and invasiveness. It is well established that cancer cells metastasize or traffic in response to chemokines just as leukocytes do. Finally, quantitative examination of leukocyte infiltrates have revealed, for example, that tumor associated macrophages (TAMs) and lymphocytes make up to 50% of the cell mass in breast carcinomas (Leek *et al.*(1997) *Cancer Res. 56*:4625-4629). These TAMs are differentiated from infiltrating monocytes and are then modified in the tumor microenvironment to secrete several growth factors for tumor progression, angiogenesis and metastasis. The TAMs then proliferate in situ. The tumor and TAMs thus considered a subgroup of inflammatory cells. Initiation, promotion and progression mark three identifiable phases of tumorigenesis. The initiation phase involves infectious, environmental and genetic alterations. The next two phases involve cross-talk between the tumorigenic, inflammatory and the immune systems with a pivotal role for chemokines. Tumor cell transcription factors (e.g., NF-kappa-β) are activated allowing the upregulation of proinflammatory mediators including growth factors, cytokines and chemokines. Both tumor and leukocyte cell-derived growth factors, proinflammatory mediators, metalloproteinases and the other cytotoxic soluble mediators regulate tumor angiogenesis, leukocyte recruitment to the tumor microenvironment and metastasis. These events involve complex patterns of communication between tumor cells, leukocytes and tissue resident cells facilitated in great part by the chemokine messaging system. The data presented in the Declarations evidence this as well as the activity of the conjugates.

In Nelson v. Bowley, the Court of Customs and Patent Appeals held that tests establishing pharmacological activity, such as the stimulation of smooth muscle tissue from gerbil colons and the modulation of the blood pressure in rats, manifest a practical utility "even though they may not establish a specific therapeutic use." 206 USPQ 881 (CCPA 1980); In re Bundy 209 USPQ 48 (CCPA 1981). Hence the data clearly establishes sufficient utility for claims to the conjugates and nucleic acids encoding them. In In re Hartop, 311 F.2d 249, 135 USPQ 419, 426-7 (CCPA 1962), the Court held that, when one skilled in the art would accept a particular test or experiment as being reasonably predictable that a tested invention would operate as alleged or have the utility alleged, the burden on behalf of an

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applicant to show utility had been satisfied. The Court went on to note that Congress has assigned the task of protecting the public from the advertising, use and sale of harmful drugs to the Food and Drug Administration, and the Federal Trade Commission, not the U.S. Patent and Trademark Office.

The Declarations establish that conjugates possess activity in the mouse xenograft models and in recognized *in vitro* assays. This showing establishes a pharmacological utility. Thus, there is no evidence of record to doubt that there is a correlation between *in vitro* data and an *in vivo* activity and effectiveness of the conjugates for treatment. A rigorous or an invariable exact correlation is not required. MPEP § 2164.02; and *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985). In *In re Brana*, the PTO had provided references that merely questioned the accuracy of *in vivo* murine tests in predicting results in humans. The references did not show that one of skill in the art would question the claimed utility of the compounds. (51F.3d 1560, 34 USPQ 2d. 1436 (Fed. Cir. 1995)).

In the present case, Applicant has provided data in the specification as filed showing functional activity of a conjugate (i.e., OPL98110) *in vitro* that supports the claims (i.e., a working example). Further, *in vitro* assays have been utilized since the mid-1980's to detect and measure chemotaxis, or inhibition thereof. The conjugate works on T-lymphocytes shows the specificity of the conjugate relative to one type of leukocyte and the Tables provide examples of other chemokines that target other leukocytes. The conjugates are designed to be targeted only to cells that express the particular chemokine receptor. Any particular conjugate will not be targeted to all activated immune effector cells, but only to those that express the particular receptor.

Further, the courts have made clear that the claim scope does not necessarily have to be limited to only those embodiments actually disclosed in the specification, and that broad claims can be supported without even a single disclosed embodiment as discussed above. *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (C.C.P.A. 1970); and *Spectra-Physics Inc. v. Coherent Inc.*, 827 F. 2d 1524, 3 USPQ2d. 1737 (Fed. Cir. 1987); *Utter v. Hiraga*, 845 F.2d at 998, 6 USPQ2d at 1714. In the present case, Example 2 provides a specific *in vitro* working example, and the specification as a whole (as supported by the state of the art) provides a much broader description that enables the currently claimed methods.

In the present case, the specification, which teaches how to prepare a multitude of conjugates, and the Declarations, Schuh *et al.* and Brühl *et al.* references, which demonstrate that conjugates containing at least six different chemokines target cells that

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express receptors for that chemokine and the conjugates inhibit or deplete such cells *in vitro* and *in vivo*. This evidence taken together, provides a more than sufficient basis for a generic claim. Further, the Examiner has not provided any objective references to show that one skilled in the art would question the teachings of the examples provided. Thus, it respectfully is submitted, that the specification as written provides sufficient guidance as to "how to use" the claimed conjugates in the recited methods. MPEP 2164.01(c). The specification *does* provide working examples illustrating the operability of the claimed method or product *as well as* a discussion of the broad terminology in the specification. *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ 2d. 1510, 1513 (Fed. Cir. 1993). [Emphasis added]

Further, the courts have held that "[e]vidence showing substantial activity against experimental tumors in mice in tests customarily used for the screening of anticancer agents of potential utility in the treatment of humans is relevant to utility in humans and is not to be disregarded." *In re Jolles*, 628 F.2d at 1327, 206 USPQ at 890 (C.C.P.A. 1980). Thus, in spite of the Examiner's assertion that no *in vivo* human data was provided, correlation of the *in vitro* data to *in vivo* mouse data in an art-accepted model has been provided by Schuh et al. and illustrates a working example of the claimed subject matter. The Examiner has not provided any objective references or scientific reasoning to establish a case that at least 50% (i.e., a preponderance) of the data known in the art would lead one skilled in the art to conclude that the RANTES-PE38 conjugate could not be extrapolated to other situations in view of the references discussed above and the art of immunotoxins as a whole in view of the teachings of the specification. The Patent Office in its own guidelines for compliance with 35 U.S.C. §112, and 35 U.S.C. §101 states that in accord with the governing case law human data is *not* required.

Additionally, the Examiner has also not provided any objective evidence showing that the conjugates would not function as described. . Thus, the burden of proof for enablement has been met.

Further, it respectfully is submitted that the specification need not disclose *every* conjugate or test every conjugate for activity to enable the genus as claimed. MPEP § 2173.05(a). A disclosure can still comply with the requirements of § 112 even if it leaves some technical problems unresolved so long as one of skill in the art could resolve them in reasonable time. *In re Hawkins*, 486 F.2d 569, 179 USPQ 157 (CCPA 1973). The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *In re Certain Limited-Charge Cell Culture Microcarriers*,

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221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd. sub nom., Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985). Further, when an Examiner decides that evidence submitted in a Declaration is insufficient, general statements directed to lacking validity or the evidence is not commensurate with the scope of the claims without an explanation supporting such findings is insufficient. MPEP § 716.01. In the present case, the Declarations provide objective data supporting the broad disclosure in the specification and the claims. Further, the Examiner has not provided a preponderance of evidence in the form of objective evidence/references in support of the reasoning set forth in the rejection to indicate that the disclosure the specification, data provided in the Declaration and the art publications, *as a whole*, are insufficient to enable the claims/

The Examiner states at page 4 of the Office Action that:

> due to the scope of 'targeted agent,' which reads on more than toxins, it can be easily seen how a lack of guidance and working examples of these 'agents' can be extrapolated to these 'non-toxin' agents.

This basis for rejection only is pertinent to claim 35. Claims 29 and 72 recite that the "targeted agent or portion thereof, when internalized in a cell, alters metabolism or gene expression in the cell, regulates or alters protein synthesis in the cell, inhibits proliferation of the cell or kills the cell." Claim 40 recites that the agent is such that migration or proliferation is inhibited, and claim 86 recites that the agent is a toxin. Only claim 35 does not recite that the agent is a toxic agent. Claim 35 is directed to a method for internalizing an agent into a cell. Claim 35 reads on *in vivo* and *in vitro* delivery and only requires internalization of the conjugate and linked agent. Internalization of the conjugate, which has been demonstrated. It is not relevant to the claimed method what is delivered into the cell. In addition, the specification, provides non-toxic agents, including therapeutics, such as nucleic acids. The specification provides details regarding delivery of nucleic acid molecules.

Furthermore, Applicant is not required to provide working examples of all "agents" or describe each and every type of agent if the knowledge in the field, in supplement to the specification, is sufficient to enable one skilled in the art to practice the claims as currently recited. The scope of enablement is that which is disclosed in the specification plus the scope of what would be known to one of skill in the art without undue experimentation. *National Recovery Technologies, Inc. v. Magnetic Separation Systems, Inc.*, 166 F. 3d 1190, 49 USPQ 2d 1671 (Fed. Cir. 1999). In the present case, based on the state of the art at the time the application was filed, the skilled artisan could, with a *reasonable and routine* amount of

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experimentation, determine if a disease or condition was mediated by activated leukocytes and determine the appropriate chemokine-toxin conjugate. Thus, the claimed methods have been enabled through broad terminology and illustrative examples (i.e., objective enablement). *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ 2d. 1510, 1513 (Fed. Cir. 1993).

It is improper to conclude that a disclosure is not enabling based on an analysis of only one of the above factors while ignoring one or more of the others. The analysis must consider all of the evidence related to each of these factors, and any conclusion of non-enablement must be based on the evidence as a whole. *In re Wands*, 858 F.2d at 737, 740, 8 USPQ2d at 1404, 1407; and MPEP § 2164.01(a). It respectfully is submitted that in view of a consideration of all of the Wands factors, the claims are enabled across the entire breadth of the claims.

The Examiner states at page 6 of the Office Action that: "[t]he bar for enablement, respectfully, is 'make and use' not 'make and test'," and states:

> The Examiner was simply taking a quote from the decision to drive the point home that (1) benefit does not currently exist in the present form (2) the field is, in fact, broad and (3) a patent is not a hunting license. These points can correctly be made under an issue of enablement aside from utility. As stands, Applicants' invention is not enabled for the full breadth of the claims as discussed throughout this rejection, wherein certain pertinent phrases were only being summarized in the Examiner's statement of Brenner.

Applicant respectfully disagrees for the reasons of record and those cited herein. Applicant has demonstrated how to make the conjugates. As discussed above, the specification teaches preparation of conjugates as fusion proteins, as chemical conjugates and provides the sequences of numerous toxins and chemokines. There are twelve working examples. In addition, the specification teaches how to isolated and formulate and administer the conjugates. The specification teaches how to identify particular chemokine targeting agents for particular diseases based upon the receptor expressed on a cell type active in a disease. The specification describes the receptors that are expressed, those of skill in the art were familiar with such information, the specification describes numerous diseases and the immune effector cells involved, and the Declaration demonstrates that those of skill in the art knew the role of such cells in at many disease states. Hence the specification provides the conjugates in currently available form. One of skill in the art is not provided with a hunting license, but merely has to follow the teachings in the specification. This is evidenced by the subsequent publications of Shuh *et al.*, and Brühl *et al.*, which each employed conjugates described in the instant application for the purpose described in the instant application.

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As discussed extensively herein and previously, Applicant has demonstrated that the conjugates target immune effector cells and inhibit their proliferation or migration.. As discussed above, conjugates have been used to deplete cells *in vivo*. Furthermore, depletion of immune effector cells is known to be effective for treating diseases involving an inflammatory component. Further, the specification describes the underlying scientific theory and describes how to select a chemokine for a particular use. The Declarations of record and the examples in the specification as acknowledged by the Examiner establish that the conjugates exhibit biological activity in recognized assays. Thus, a biological utility adequate to support a utility has been demonstrated. MPEP § 2164.07. Furthermore, this utility coupled with all of the teachings in the specification regarding how to select a chemokine targeting agent and how to administer it are more than adequate to demonstrate how to use the conjugates in the current method claims. Therefore, the recitation of *Brenner v. Manson* even by analogy (or metaphorically) is inapt.

If a statement of utility in the specification contains within it a connotation of how to use and/or the art recognizes that standard modes of administration are known and contemplated, 35 U.S.C 112 is satisfied. *In re Johnson*, 282 F.2d 370, 373, 127 USPQ 216, 219 (CCPA 1960); *In re Hitchings*, 342 F.2d 80, 87, 144 USPQ 637, 643 (CCPA 1965). See also *In re Brana*, 51 F.2d 1560, 1566, 34 USPQ2d 1437, 1441 (Fed. Cir. 1993). In the present case, Applicant has not only provided a connotation of how to use the conjugates in the claimed methods, but also has demonstrated by the references of record (e.g., Schuh et al. and Brühl et al.) that such conjugates target immune effector cells as described in the specification and claimed (i.e., how to use).

Conclusions

In light of the extensive teachings and working examples in the specification, the knowledge of those of skill in the art and the high level of skill in the art, the breadth of the claims, the predictability of the methods, it would not require undue experimentation to make and use the conjugates as claimed in claims 29 and 72 as well as claims 40 and 35. Claim 86, as noted is outside the purview of this rejection. Furthermore, the Examiner, has not considered dependent claims or claims 40, which are of different scope. It respectfully is submitted that one of skill in the art could readily make and use conjugates for inhibiting the proliferation, migration or activity of secondary tissue damage-promoting inflammatory cells without undue experimentation. Furthermore, one of skill in the art could readily practice the method of claim 35, which only requires selection of a chemokine receptor targeting agent

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and linking it to an agent for internalization by a cell bearing the receptor. The Declarations of record clearly demonstrate this.

The Examiner appears to urge that if there is *any* experimentation involved in determining whether a disease state or condition is mediated by inappropriate triggering, dis-regulation or over-activation of the immune response, the claims are not enabled. The Courts have established that a disclosure can comply with the requirements of § 112 even if it leaves some technical problems unresolved so long as one of skill in the art could resolve them in reasonable time. *In re Hawkins*, 486 F.2d 569, 179 USPQ 157 (C.C.P.A 1973). Further, "a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (quoting *Ex parte* Jackson, 217 USPQ 804,807 (Bd. App. 1982).

As discussed any experimentation to identify the chemokine and chemokine receptors associated associate with cells present in a particular disease or condition, to design conjugate having the components of the chemokine and toxin/non-toxin, and administering the conjugate or contacting cells with the conjugate to effectively alter metabolism or gene expression in the targeted cell, regulate or alter protein synthesis in the targeted cell, inhibit proliferation of the targeted cell or kill the targeted cell would not be undue.

Fairness

Applicant is entitled to claims that are commensurate in scope not only with what applicant has specifically described and exemplified, but commensurate in scope with that which one of skill in the art could obtain by virtue of that which the applicant has disclosed. In this instance, applicant has disclosed and taught generic methods and products as well as individual species thereof. It is unfair and unduly limiting to require applicants to limit the claims, when the application clearly teaches how to make and use the full scope of the products in the claimed methods. The specification clearly places those of skill in the art in possession of a larger genus; the specification discloses a large number of chemokines and targeted agents and provides sequences or sources therefore; and preparing the conjugates is routine. To so limit the claims to only to the a few of the exemplified species is also contrary to the public policy upon which the U.S. patent laws are based to require applicant to limit the claims. See, for example, *In re Goffe*, 542 F.2d 801, 166 USPQ 85 (CCPA 1970):

> for the Board to limit appellant to claims involving the specific materials disclosed in the examples so that a competitor seeking to avoid infringing the

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claims can merely follow the disclosure and make routine substitutions "is contrary to the purpose for which the patent system exists - to promote progress in the useful arts."

The public purpose on which the patent law rests requires the granting of claims commensurate in scope with the disclosure. This requires as much the granting of broad claims on broad inventions as it does the granting of more specific claims on more specific inventions. *In re Sus and Schafer*, 49 CCPA 1301, 306 F.2d 494, 134 USPQ 301, at 304. If applicant is required to limit the claims as suggested by the Examiner, then those of skill in the art can, by virtue of the teachings of this application, select chemokines and prepare conjugates that inhibit proliferation, migration or activation of immune cells, thereby practicing what is disclosed in the application, but avoid infringing such limited claims. The instant application teaches a broader modality and products for inhibiting proliferation, activation or migration of immune cells; and having done so, places the public in possession of such knowledge. Having provided this disclosure, it permits others to benefit therefrom. Those of skill in the art should not be permitted to practice what is taught in the application, but avoid infringing the claims. To permit that is simply not fair. It will permit those of skill in the art to prepare conjugates for treating diseases that involved immune effector cells, but not infringe the claims. Potential infringers, exemplified by Schuh *et al.*. and Brühl *et al.*, who prepared conjugates exactly as taught in the specification for the same purpose described in the application, evidence that this is not idle speculation. Small early stage innovative companies can ill-afford to dedicate their innovations to the public.

* * *

Therefore, in view of the above, reconsideration and allowance of the application are respectfully requested.

Respectfully submitted,

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FORM PTO-1449 (Modified)	ATTY. DOCKET NO. 25020-601B	SERIAL NO. 09/360,242
LIST OF PATENTS AND PUBLICATIONS FOR APPLICANT'S INFORMATION DISCLOSURE STATEMENT	APPLICANT MCDONALD et al.	
	FILING DATE 07/22/99	GROUP ~~1646~~ 1647

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U.S.PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER							DATE	NAME	CLASS	SUB CLASS	FILING DATE
BL	AA	5	3	4	6	6	8	6	09/13/94	Lyle *et al.*	424	1.41	10/02/92
BL	AB	5	4	1	3	7	7	8	05/09/95	Kunkel *et al.*	424	1.41	10/05/92
BL	AC	5	5	7	6	2	8	8	11/19/96	Lappi *et al.*	514	002	06/10/94
BL	AD	5	6	3	3	1	4	9	05/27/97	Guegler *et al.*	435	69.5	12/07/94
BL	AE	5	6	4	8	3	3	4	07/15/97	Davis *et al.*	514	12	05/24/95
BL	AF	5	9	1	0	4	3	1	06/08/99	Ni *et al.*	435	69.5	03/19/97
BL	AG	6	0	0	1	6	4	9	12/24/99	Caput *et al.*	435	365.1	09/29/92

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER							DATE	COUNTRY	CLASS	SUB CLASS	Translation Yes	Translation No
BL	AH	9	0	1	2	5	9	7	11/01/90	PCT				
BL	AI	9	1	1	8	0	1	2	11/28/91	PCT				
BL	AJ	9	3	2	3	0	6	2	11/25/93	PCT				X
BL	AK	9	4	0	7	5	3	5	04/14/94	PCT				
BL	AL	9	4	0	7	5	4	2	04/14/94	PCT				
BL	AM	9	5	1	2	4	1	4	05/11/95	PCT				
BL	AN	0	0	0	4	9	2	6	02/03/00	PCT				

*English language abstract provided on cover of patent

OTHER ART (Including Author, Title, Date, Pertinent Pages, Etc.)

EXAMINER [signature] | DATE CONSIDERED 02/18/07

EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

FEB 22 2007

PTO-1449 (Modified)

LIST OF PATENTS AND PUBLICATIONS FOR APPLICANT'S INFORMATION DISCLOSURE STATEMENT

ATTY. DOCKET NO.	SERIAL NO.
25020-601B	09/360,242
APPLICANT	
MCDONALD et al.	
FILING DATE	GROUP
07/22/99	~~1646~~ 1647

BL	AO	Abstract No. XP000881561, P. Roby, et al., Melanoma-specific cytotoxicity of a human MGSA/GROalpha C-terminal peptide conjugated to daunorubicin, *Oncology Reports, 3:*1777-178 discussion (1996).
BL	AP	Abstract No. XP000881538, Ray, E., et al., Receptor mediated endocytosis of IL-8: a fluorescent microscopic evidence and implication of the process in ligand induced biological response in human neutrophils, *Cytokine, 9*(8):587-569 (1997).
BL	AQ	al-Jaufy, A.Y., et al., Purification and characterization of a Shiga toxin A subunit-CD4 fusion protein cytotoxic to human immunodeficiency virus-infected cells, *Infect. Immun., 63:*3073-8 (1995).
BL	AR	al-Jaufy, A.Y., et al., Cytotoxicity of a shiga toxin A subunit-CD4 fusion protein to human immunodeficiency virus-infected cells, *Infect. Immun., 62:*956-60 (1994).
BL	AS	Albini *et al.*, HIV-1 tat protein mimicry of chemokines, *Proc. Natl. Acad. Sci. USA* 95:13153-13158 (1998)
BL	AT	Baldwin, G.C., et al., *Blood, 11:*3279-82 (1993).
BL	AU	Barbieri, L., et al., Polynucleotideadenosine glycosidase activity of ribosome-inactivating proteins: effect on DNA, RNA and poly(A), *Nucleic Acids Res., 25:*518-22 (1997).
BL	AV	Barthelemy, I., et al., The expression of saporin, a ribosome-inactivating protein from the plant Saponaria officinalis, in Escherichia coli., *J. Biol. Chem., 268:*6541-8 (1993).
BL	AW	Battelli, M.G., et al., Toxicity of ribosome-inactivating proteins-containing immunotoxins to a human bladder carcinoma cell line, *Int. J. Cancer, 65:*485-90 (1996).
BL	AX	Beall, C.J., et al., Site-directed mutagenesis of monocyte chemoattractant protein-I identifies two regions of the polypeptide essential for biological activity, *Biochem. J., 313:*633-40 (1996).
BL	AY	Benveniste, E.N., Cytokine circuits in brain. Implications for AIDS dementia complex, *Res. Publ. Assoc. Res. Nerv. Ment. Dis., 72:*71-88 (1994).
BL	AZ	Bergamaschi, G., et al., Saporin, a ribosome-inactivating protein used to prepare immunotoxins, induces cell death via apoptosis, *Br. J. Haematol., 93:*789-94 (1996).
BL	BA	Bolognesi, A., et al., New ribosome-inactivating proteins with polynucleotideadenosine glycosidase and antiviral activities from Basella rubra L. and bougainvillea spectabilis, *Willd. Planta, 203:*422-9 (1997).
BL	BB	Bolognesi, A., et al., Induction of apoptosis by ribosome-inactivating proteins and related immunotoxins, *Int. J. Cancer, 68:*349-55
BL	BC	Bonini, J.A., et al., Cloning, expression, and chromosomal mapping of a novel human CC-chemokine receptor (CCR10) that displays high-affinity binding for MCP- I and MCP-3, *DNA Cell Biol., 16:*1249-56 (1997).
BL	BD	Book, A.A., et al., 192 IgG-saporin: 2. Neuropathology in the rat brain, *Acta Neuropathol., 89:*519-26 (1995).

EXAMINER [signature] | DATE CONSIDERED 12/18/06

EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

FEB 22 2007

PTO-1449 (Modified)	ATTY. DOCKET NO. 25020-601B	SERIAL NO. 09/360,242
LIST OF PATENTS AND PUBLICATIONS FOR APPLICANT'S INFORMATION DISCLOSURE STATEMENT	APPLICANT MCDONALD et al.	
	FILING DATE 07/22/99	GROUP ~~1646~~ 1647

BL	BE	Book, A.A., et al., 192 IgG-saporin: I. specific lethality for cholinergic neurons in the basal forebrain of the rat, *J. Neuropathol. Exp. Neurol., 53*:95-102 (1994).
BL	BF	Boulay, J.L., et al., The interleukin-4 family of lymphokines, *Curr. Opin. Immunol.*, 4:294-8 (1992).
BL	BG	Brigotti, M., et al., The RNA-N-glycosidase activity of Shiga-like toxin I:kinetic parameters of the native and activated toxin, *Toxicon., 35:*1431-7 (1997).
BL	BH	Brinkmann, U., et al., Immunotoxins against cancer, *Biochim. Biophys. Acta, 1198*:27-45 (1994).
BL	BI	Challita-Eid, P.M., et al., A RANTES-antibody fusion protein retains antigen specificity and chemokine function, *J. Immunol., 161:*3729-36 (1998).
BL	BJ	Chandler, J.C., et al., Genetic engineering of immunotoxins, *Semin. Pediatr. Surg., 5*:206-11 (1996).
BL	BK	Chandler, L.A., et al., Targeting tumor cells via EGF receptors:selective toxicity of an HBEGF-toxin fusion protein, *Int. J. Cancer, 78:*106-11 (1998).
BL	BL	Christie, R.H., *J. Neuropthol. Exp. Neurol., 55:*491-8 (1996).
BL	BM	Christophers, E., et al., Psoriasis: mechanisms and entry points for possible therapeutic inverventions, *Australas J. Dermatol., 37 Suppl. I:*S4-6 (1996).
BL	BN	Clark-Lewis, I., et al., Structure-activity relationships of chemokines, *J. Leukoc. Biol., 57:*703-11 (1995).
BL	BO	Crowe, S.M., GM-CSF and its effects on replication of HIV-I in cells of macrophage lineage, *J. Leukoc. Biol.*, 62:41-8 (1997).
BL	**BP**	**Debinski**, W., et al., An immunotoxin with increased activity and homogeneity produced by reducing the number of lysine residues in recombinant Pseudomonas exotoxin, *Bioconjug. Chem., 5*:40-6 (1994).
BL	BQ	Essand, M., et al., Anti-prostate immunotoxins:cytotoxicity of E4 antibody-Pseudomonas exotoxin constructs, *Int. J. Cancer, 77*:123-7 (1998).
BL	BR	Gebicke-Haerter, P.J., et al., Rat microglial interleukin-3, *J. Neuroimmunol., 50*:203-14 (1994).
BL	BS	Ghetie, V., et al., *Pharmac. Ther., 63:*209-34 (1994).
BL	BT	Giulian, D., et al., The role of mononuclear phagocytes in wound healing after traumatic injury to adult mammalian brain, *J. Neurosci., 9*:4416-29 (1989).
BL	BU	Glabinski, A.R., et al., Central nervous system chemokine mRNA accumulation follows initial leukocyte entry at the onset of acute murine experimental autoimmune encephalomyelitis, *Brain Behav. Immun., 9*:315-30 (1995).
BL	BV	Gonzalo *et al.*, Eosinophil recruitment to the lung in a murine model of allergic inflammation, *J. Clin. Invest.* 98(10):2332-2345 (1996)

EXAMINER [signature] | DATE CONSIDERED 12/18/02

EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

FEB 22 2007

LIST OF PATENTS AND PUBLICATIONS FOR APPLICANT'S INFORMATION DISCLOSURE STATEMENT	25020-601B	09/360,242
	APPLICANT MCDONALD et al.	
	FILING DATE 07/22/99	GROUP ~~1648~~ 1647

	BW	Gottlieb, S.L., et al., Response to psoriasis to a lymphocyte-selective toxin (DAB389IL-2) suggests a primary immune, but not keratinocyte, pathogenic basis, *Nat. Med. 1*:442-7 (1995).
	BX	Hoang, T., et al., *J. Biol. Chem., 268*:11881-7 (1993).
	BY	Husain, S.R., et al., Complete regression of establilshed human glioblastoma tumor xenograft by interleukin-4 toxin therapy, *Cancer Res., 58*:3649-53 (1998).
	BZ	Jose, P.J., et al., Eotaxin: cloning of an eosinophil chemoattractant cytokine and increased mRNA expression in allergen-challenged guinea-pig lungs, *Biochem. Biophys. Res. Commun., 205:*788-94 (1994).
	CA	Keppler-Hafkemeyer, et al., Role of caspases in immunotoxin-induced apoptosis of cancer cells, *Biochemistry, 37*:16934-42 (1998).
	CB	King, C.R., et al., The performance of e23(Fv)PEs, recombinant toxins targeting the erbB-2 protein, *Semin. Cancer Biol., 7*:79-86 (1996).
	CC	Kloss, C.U., et al., Proliferation of ramified microglia on as astrocyte monolayer: characterization of stimulatory and inhibitory cytokines, *J. Neurosci Res.*, 49:248-54 (1997).
	~~CD~~	~~Kreitman and Pastan, *Semin. Cancer Biol.* 6(5):297-306 (1995)~~
	CE	Kreitman, R.J., et al., Recombinant toxins containing human granulocyte-macrophage colony-stimulating factor and either pseudomonas exotoxin or diphtheria toxin kill gastrointestinal cancer and leukemia cells, *Blood, 90*:252-9 (1997).
	~~CF~~	~~Kreitman, R.J., et al., Recombinant toxins, *Adv. Pharmacol., 28*:193-219 (1994).~~
	CG	Lappi, D.A., et al., Expression and activities of a recombinant basis fibroblast growth factor-saporin fusion protein, *J. Biol. Chem., 269:*12552-8 (1994).
	CH	Lappi, D.A., et al., Characterization of a saporin mitotoxin specifically cytotoxic to cells bearing the granulocyte-macrophage colony-stimulating factor receptor, *Growth Factors, 9*:31-9 (1993).
	CI	Lappi, D.A., et al., Mitotoxin: growth factor-targeted cytotoxic molecules, *Prog. Growth Factor Res., 2*:223-36 (1990).
	CJ	Lee, S.C., et al., Cytokine production by human fetal microglia and astrocytes. Differential induction by lipopolysaccharide and IL-I beta. *J. Immunol.*, 150:2659-67 (1993).
	CK	MacDonald *et al.*, Spliced mRNA encoding the murine cytomegalovirus chemokine homolog predicts a β chemokine of novel structure, *J. of Virology* 73(5):3682-3691 (1999)
	CL	Mantyh, P.W., et al., Inhibition of hyperalgesia by ablation of lamina I spinal neurons expressing the substance P receptor, *Science, 278:*275-9 (1977).
	CM	Matsumoto *et al.*, Pivotal role of interleukin-8 in the acute respiratory distress syndrome and cerebral reperfusion injury, *J. of Leukocyte Biology* 62:581 (1997)
	CN	Mayne, M., et al., HIV-I tat molecular diversity ad induction of TNF-alpha: implications for HIV-induced neurological disease, *Neuroimmunomodulation, 5*:184-92 (1988).

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EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

FEB 22 2001

PTO-1449 (Modified)	ATTY. DOCKET NO 25020-601B	SERIAL NO. 09/360,242
LIST OF PATENTS AND PUBLICATIONS FOR APPLICANT'S INFORMATION DISCLOSURE STATEMENT	APPLICANT MCDONALD et al.	
	FILING DATE 07/22/99	GROUP ~~1646~~ 1647

BL	CO	McDonald, J.R., et al., Large-scare purification and characterization of recombinant fibroblast growth factor-saporin mitotoxin, *Protein Expr. Purif., 8*:97-108 (1996).
~~BL~~	~~CP~~	~~Medh, J.D., et al., *J. Biol. Chem., 270*:536-540(1995).~~
BL	CQ	Mock and Pugsley, The BtuB group Co1 plasmids and homology between the colicins they encode, *J. of Bacteriology* 150(3):1069-1076(1982)
BL	CR	Novella, A., et al., Expression of adhesion molecules and functional stimulation in human neutrophils: modulation by GM-CSF and role of the Bcr gene, *Br. J. Haematol.*, 98:621-6 (1997).
BL	CS	**P. Roby**, et al., Melanoma-specific cytotoxicity of a human MGSA/GROalpha C-terminal peptide conjugated to daunorubicin, *Oncology Reports, 3*:175-179 (1996).
BL	CT	Panchagnula, R., et al., Monoclonal antibodies in drug targeting, *J. Clin. Pharm. Ther., 22*:7-19 (1997).
BL	CU	Puri, R.K., et al., Preclinical development of a recombinant toxin contaiing circularly permuted interleukin 4 and truncated Pseudomonas exotoxin for therapy of malignant astrocytoma, *Cancer Res., 56*:5631-7 (1996).
BL	CV	Puri, R.K., et al., Targeting of interleukin-13 receptor on human renal cell carcinoma cells by a recombinant chimeric protein composed of interleukin-13 and a truncated form of Pseudomonas exotoxin A (PE38QQR), *Blood, 87*:4333-9 (1996).
~~BL~~	~~CW~~	~~Puri, *Toxicol. Pathol.* 27(1):53-57 (1999)~~
BL	CX	Ransohoff, R.M., et al., Chemokines and chemokine receptors in model neurological pathologies:molecular and immunocytochemical approaches, *Methods Enzymol., 287*:319-48 (1997).
BL	CY	**Ray**, E., et al., Receptor mediated endocytosis of IL-8: a fluorescent microscopic evidence and implication of the process in ligand induced biological response in human neutrophils, *Cytokine, 9*(8):587-569 (1997).
BL	CZ	Reiter, Y., et al., Peptide-specific killing of antigen-presenting cells by a recombinant antibody-toxin fusion protein targeted to major histocompatibility complex/peptide class I complexes with T cell receptor-like specificity, *Proc. Natl. Acad. Sci., 94*:4631-6 (1997).
BL	DA	Roncuzzi, L., et al., DNA-nuclease activity of the single-chain ribosome-inactivating proteins dianthin 30, saporin 6 and gelonin, *FEBS Lett., 392*:16-20 (1996).
BL	DB	Rosemuller, H., et al., Treatment of acute myelocytic leukemia with interleukin-6 Pseudomonas exotoxin fusion protein in a rat leukemia model, *Leukemia, 10*:1796-803 (1996).
BL	DC	Rossner, S., et al., Cholinergic immunolesions by 1921gG-saporin--useful tool to simulate pathogenic aspects of Alzheimer's disease, *Int. J. Dev. Neurosci., 18*:835-50 (1997).
BL	DD	Rozemuller, H., et al., Sensitivity of human acute myeloid leukaemia to diphtheria toxin-GM-CSF fusion protein, *Br. J. Haematol., 98*:952-9 (1997).

EXAMINER	DATE CONSIDERED 12/15/00

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FEB 22 2001

TO-1449 (Modified)	ATTY. DOCKET NO. 25020-601B	SERIAL NO. 09/360,242
LIST OF PATENTS AND PUBLICATIONS FOR APPLICANT'S INFORMATION DISCLOSURE STATEMENT	APPLICANT MCDONALD et al.	
	FILING DATE 07/22/99	GROUP ~~1646~~ 1647

BL	DE	Rucker *et al.*, Utilization of chemokine receptors, orphan receptors, and herpesvirus-encoded receptors by diverse human and simian immunodeficiency viruses, *J. of Virology* 71(12):8999-9007 (1997)
BL	DF	Satyamurthy, P., et al., *Proteins: structure, function and genetics, 19:*340-2 (1994).
BL	~~DG~~	~~Sawada, M., et al., *Neurosci. Lett., 160:*131-4 (1993).~~ OK RL 12/15/10
BL	DH	Schall, T.J., et al., Chemokines, leukocyte trafficking, and inflammation, *Curr. Opin. Immunol., 6:*865-73 (1994).
BL	DI	Sibille and Reynolds, Macrophages and polymorphonuclear neutrophils in lung defense and injury, *Am. Rev. Respir. Dis.* 141:471-501 (1990)
BL	DJ	Siegall, C.B., et al., Targeted toxins as anticancer agents, *Cancer, 74:*1006-12 (1994).
BL	**DK**	**Silbert**, D.I., Glycosaminoglycans of bovine aorta endothelial cells: Identification and localization by use of a platelet factor 4-fluorescein probe, *Journal of Histochemistry and Cytochemistry, 38*(4):589-593 (1990).
BL	DL	Skinner, L.M., et al., Investigation of ribosome binding by the Shiga toxin AI subunit, using competition and site-directed mutagenesis, *J. Bacteriol., 179:*1368-74 (1997).
BL	DM	Skinner, L.M., et al., Inhibition of prokaryotic translation by the Shiga toxin enzymatic subunit, *Microb. Pathog. 24:*117-22 (1998).
BL	DN	Steitz, S.A., et al., Mapping of MCP-I functional domains by peptide analysis and site-directed mutagenesis, *FEBS Lett., 430:*158-64 (1998).
BL	DO	Stirpe, F., et al., Ribosome-inactivating proteins from plants:present status and future prospects, *Biotechnology (NY), 10:*405-12 (1992).
BL	~~DP~~	~~Stirpe, F., et al., *J. Biol. Chem., 255:*6947-6953 (1980).~~ ok RL 12/15/10
BL	DQ	Strieter and Kunkel, Acute lung injury the role of cytokines in the elicitation of neutrophils, *J. of Investigative Medicine* 42(40:640 (1994)
BL	DR	Suh, J.K., et al., Shiga toxin attacks bacterial ribosomes as effectively as eucaryotic ribosomes, *Biochemistry, 37:*9394-8 (1998).
BL	DS	Suzumura, A., et al., Interleukin-4 induces proliferation and activation of microglia but suppresses their induction of class II major histocompatibility complex antigen expression, *J. Neuroimmunol., 53:*209-18 (1994).
BL	DT	Tesh, V.L., et al., Purified Shiga-like toxins induce expression of proinflammatory cytokines from murein peritoneal macrophages, *Infect. Immun., 62:*5085-94 (1994).
BL	DU	Ugoccioni, M., et al., *J. Exp. Med., 183:*2379-84 (1996).
BL	DV	Van Damme, E.J., et al., Type I ribosome-inactivating proteins are the most abundant proteins in iris (Iris hollandica var. Professor Blaauw) bulbs: characterization and molecular cloning, *Biochem. J., 324:*963-70 (1997).

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FEB 22 2011

PTO-1449 (Modified)	ATTY. DOCKET NO. 25020-601B	SERIAL NO. 09/360,242
LIST OF PATENTS AND PUBLICATIONS FOR APPLICANT'S INFORMATION DISCLOSURE STATEMENT	APPLICANT MCDONALD et al.	
	FILING DATE 07/22/99	GROUP ~~1646~~ 1647

BL	DW	Van Oijen, M.G., et al., Rationale for the use of immunotoxins in the treatment of HIV-infected humans, *J. Drug Target, 5*:75-91 (1998).
BL	DX	Ward, S.G., et al., Chemokines: understanding their role in T-lymphocyte biology, *Biochem J.*, 333:457-70 (1998).
BL	DY	Waurzyniak, B., et al., In vivo toxicity, pharmacokinetics, and antileukemic activity of TXU (Anti-CD7)-pokeweed antiviral protein immunotoxin, *Clin. Cancer Res., 3*:881-90 (1997).
BL	DZ	Welbourn and Young, Endotoxin, septic shock and acute lung injury: neutrophils, macrophages and inflammatory mediators, *Br. J. Surg.* 79:998-1003 (1992)
BL	EA	Wiley, R.G., et al., Destruction of neurokinin-I receptor expressing cells in vitro and in vivo using substance P-saporin in rats, *Neurosci. Lett., 230*:97-100 (1997).
BL	EB	Wiley, R.G., et al., Targeting toxins to neural antigens and receptors, *Semin. Cancer Biol., 7*:71-7 (1996).
BL	EC	Windsor *et al.*, Role of the neutrophil in adult respiratory distress syndrome, *Br. J. Surg.* 80:10-17 (1993)
BL	ED	Wu, M., et al., Are immunoconjugates useful for therapy with autoimmune diseases?, *Int. J. Immunopharmacol., 19*:83-93 (1997).
BL	EE	Yang, D., et al., Recombinant heregulin-Pseudomonas exotoxin fusion proteins:interactions with the heregulin receptors and antitumor activity in vivo, *Clin. Cancer Res., 4*:993-1004 (1998).
BL	EF	Ying *et al.*, Enhanced expressin of eotaxin and CCR3 mRNA and protein in atopic asthma. Association with airway hyperresponsiveness and predominant co-localization of eotaxin mRNA to bronchial epithelial and endothelial cells, *Eur. J. Immunol.* 27:3507-3516 (1997)
BL	EG	Yoshie, O., et al., Novel lymphocyte-specific CC chemokines and their receptors, *J. Leukoc. Biol., 62*:634-44 (1997).
BL	EH	Youle, R.J., et al., Immunotoxins for central nervous system malignancy, *Semin. Cancer Biol., 7*:65-70 (1996).
BL	~~EI~~	~~Zheng, G., et al., *J. Histochem. Cytochem., 42*:531-42 (1994).~~ OK BL 12/18/01
BL	EJ	Zurawski, G., et al., Interleukin 13 elicits a subset of the activities of its close relative interleukin 4, *Stem Cells (Dayt)*, 12:169-74 (1994).

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FEB 22 2002

FORM PTO-1449 (Modified)	ATTY. DOCKET NO. 25020-601B	SERIAL NO. 09/360,242
LIST OF PATENTS AND PUBLICATIONS FOR APPLICANT'S INFORMATION DISCLOSURE STATEMENT	APPLICANT MCDONALD et al.	
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	DE	~~Rucker *et al.*, Utilization of chemokine receptors, orphan receptors, and herpesvirus-encoded receptors by diverse human and simian immunodeficiency viruses, *J. of Virology* 71(12):8999-9007 (1997)~~ DUPLICATES
	DF	~~Satyamurthy, P., et al., *Proteins: structure, function and genetics*, 19:340-2 (1994).~~
	DG	~~Sawada, M., et al., *Neurosci. Lett.*, 160:131-4 (1993).~~ OK MC 12/18/00 Reference considered
	DH	Schall, T.J., et al., Chemokines, leukocyte trafficking, and inflammation, *Curr. Opin. Immunol.*, 6:865-73 (1994).
	DI	Sibille and Reynolds, Macrophages and polymorphonuclear neutrophils in lung defense and injury, *Am. Rev. Respir. Dis.* 141:471-501 (1990)
	DJ	Siegall, C.B., et al., Targeted toxins as anticancer agents, *Cancer*, 74:1006-12 (1994).
	DK	Silbert, D.I., Glycosaminoglycans of bovine aortic endothelial cells: Identification and localization by use of a platelet factor 4-fluorescein probe, *Journal of Histochemistry and Cytochemistry*, 38(4):589-593 (1990).
	DL	Skinner, L.M., et al., Investigation of ribosome binding by the Shiga toxin A1 subunit, using competition and site-directed mutagenesis, *J. Basteriol.*, 179:1368-74 (1997).
	DM	Skinner, L.M., et al., Inhibition of prokaryotic translation by the Shiga toxin enzymatic subunit, *Microb. Pathog.* 24:117-22 (1998).
	DN	Steitz, S.A., et al., Mapping of MCP-I functional domains by peptide analysis and site-directed mutagenesis, *FEBS Lett.*, 430:158-64 (1998).
	DO	Stirpe, F., et al., Ribosome-inactivating proteins from plants:present status and future prospects, *Biotechnology (NY)*, 10:405-12 (1992).
	DP	~~Stirpe, F., et al., *J. Biol. Chem.*, 255:6947-6953 (1980).~~ OK MC 12/18/00 Reference considered
	DQ	Strieter and Kunkel, Acute lung injury the role of cytokines in the elicitation of neutrophils, *J. of Investigative Medicine* 42(40:640 (1994)
	DR	Suh, J.K., et al., Shiga toxin attacks bacterial ribosomes as effectively as eucaryotic ribosomes, *Biochemistry*, 37:9394-8 (1998).
	DS	Suzumura, A., et al., Interleukin-4 induces proliferation and activation of microglia but suppresses their induction of class II major histocompatibility complex antigen expression, *J. Neuroimmunol.*, 53:209-18 (1994).
	DT	Tesh, V.L., et al., Purified Shiga-like toxins induce expression of proinflammatory cytokines from murein peritoneal macrophages, *Infect. Immun.*, 62:5085-94 (1994).
	DU	Ugoccioni, M., et al., *J. Exp. Med.*, 183:2379-84 (1996). OK MC 7/12/06 Reference considered
	DV	Van Damme, E.J., et al., Type I ribosome-inactivating proteins are the most abundant proteins in iris (Iris hollandica var. Professor Blaauw) bulbs: characterization and molecular cloning, *Biochem. J.*, 324:963-70 (1997).

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FEB 22 2007

Issue Classification	Application/Control No.	Applicant(s)/Patent under Reexamination	
	09/360,242	MCDONALD ET AL.	
	Examiner	Art Unit	
	Robert Landsman	1647	

ISSUE CLASSIFICATION

ORIGINAL CLASS	ORIGINAL SUBCLASS	CROSS REFERENCE(S) CLASS	CROSS REFERENCE(S) SUBCLASS (ONE SUBCLASS PER BLOCK)
514	2	424	85.1
INTERNATIONAL CLASSIFICATION		530	402
A 0 1 N	37/18		
C 0 7 K	1/00		
C 0 7 K	14/00		
C 0 7 K	16/00		
A 6 1 K	45/00		

(Assistant Examiner) (Date)

HQ Hammell (Legal Instruments Examiner) 8/7/06 (Date)

ROBERT S. LANDSMAN, PH.D PRIMARY EXAMINER (Primary Examiner) 7-29-06 (Date)

Total Claims Allowed: 56

O.G. Print Claim(s)	O.G. Print Fig.
1	none

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
	~~1~~	5	31		~~61~~	50	91		121		151		181
	~~2~~	6	32		~~62~~	51	92		122		152		182
	~~3~~		~~33~~		~~63~~	52	93		123		153		183
	~~4~~	7	34		~~64~~	53	94		124		154		184
	~~5~~	29	35	22	65	54	95		125		155		185
	~~6~~	30	36	23	66	55	96		126		156		186
	~~7~~	8	37	24	67	56	97		127		157		187
	~~8~~		~~38~~	25	68		98		128		158		188
	~~9~~		~~39~~	26	69		99		129		159		189
	10	9	40	27	70		100		130		160		190
	~~11~~		~~41~~	28	71		101		131		161		191
	12	10	42	31	72		102		132		162		192
	~~13~~		~~43~~	32	73		103		133		163		193
	14	11	44	33	74		104		134		164		194
	15	12	45	34	75		105		135		165		195
	16	13	46	35	76		106		136		166		196
	~~17~~		~~47~~	36	77		107		137		167		197
	18	14	48	37	78		108		138		168		198
	19	15	49	38	79		109		139		169		199
	20	16	50	39	80		110		140		170		200
	21	17	51	40	81		111		141		171		201
	22	18	52	41	82		112		142		172		202
	23	19	53	42	83		113		143		173		203
	24	20	54	43	84		114		144		174		204
	25		~~55~~	44	85		115		145		175		205
2	26		~~56~~	45	86		116		146		176		206
3	27	21	57	46	87		117		147		177		207
4	28		~~58~~	47	88		118		148		178		208
1	29		~~59~~	48	89		119		149		179		209
	~~30~~		~~60~~	49	90		120		150		180		210

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